A Systematic Review Examining *Cannabis* Use for the Treatment of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a neurodegenerative disease that affects over 2 million people worldwide. MS results in disabling and troublesome symptoms due to damage to the brain and spinal cord. Pharmaceutical options exist for the management of MS and its associated symptoms. Some individuals with MS utilize *Cannabis* to help manage their symptoms. Cannabinoid use in MS animal models have shown promise, and evidence supporting the indication(s) for *Cannabis* in MS is rapidly evolving and highly relevant to clinical practice. Currently one formulation of *Cannabis* (Sativex®) has Health Canada approval as an adjunct treatment option for MS-related spasticity and pain.

A systematic review was conducted to examine the literature on *Cannabis*-based medicine (CBM) use in MS. Medline, Embase, and International Pharmaceutical Abstracts were searched for articles related to MS and CBM in February 2018. All human studies, with outcomes specific to MS, and published in English, were eligible for inclusion. There was no publication year limit and no restrictions based on study design. Articles were screened independently by two reviewers, first by title and then by abstract. Two reviewers then independently performed data extraction on all included articles, and a quality assessment using a modified Downs and Black assessment tool. Included articles were categorized by their primary outcome into the following categories: spasticity, tremor, pain, cognition, balance/walking, bladder dysfunction, general symptoms, adverse events/safety, or disease progression. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

After removal of duplicates, 2058 articles were identified, with 60 studies meeting the inclusion criteria. Twenty-six articles were randomized controlled studies and 34 utilized a non-randomized study design. Cannabidiol and delta-9-tetrahydrocannabidiol oromucosal spray (Sativex®) was the most commonly studied CBM for MS. The dose size and frequency of administration between studies was inconsistent. Spasticity was the most common MS symptom to be treated with CBM (n=29), followed by pain (n=8) and cognition (n=6). Twenty-three studies were poor quality, 14 were fair quality, and 23 were good/excellent quality. CBM showed a trend of reducing spasticity and pain in individuals with MS; however, the variable quality of the evidence requires consideration when examining results of individual studies. Adverse events were frequent but mild, and CBM was well tolerated.

This systematic review outlines the potential of CBM to treat MS spasticity and pain, however more research is needed to examine its use for other MS symptoms. Additionally, the use of other cannabinoid products for MS treatment, the effects of administering CBM with current MS medications, and possible long-term impacts of CBM in those with MS need to be investigated further.

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ABBREVIATIONS

$5HT_{1A}$	Serotonin 1A receptor
9-HPT	9-hole peg test
10/36 SRT	10/36 spatial recall test
2-AG	2-Arachidonoylglycerol
2-AGE	2-Arachidonyl glyceryl ether
5HT1A	Serotonin 1A receptor
9-HPT	9-Hole peg test
AA	Arachidonic acid
ACTH	Adrenocorticotropin hormone
AE	Adverse event
AEA	Anandamide
BBB	Blood-brain barrier
BL	Baseline
BP	Blood pressure
CAM	Complementary and alternative medicine
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBD	Cannabidiol
CBM	Cannabis-based medicine
CE	Cannabis extract
CIS	Clinically isolated syndrome
CNP	Central neuropathic pain
CNS	Central nervous system
CREAE	Chronic relapsing experimental autoimmune encephalomyelitis
CRS	Category rating scale
D2High	Dopamine D2 high receptors
DAG	Diacylglycerol
DAGL	Diacylglycerol lipase
DCP	Data collection period
DMT	Disease modifying therapy
DN4	Douleur neuropathique 4
DSM	Diagnostic and statistical manual of mental disorders
EAE	Experimental autoimmune encephalomyelitis
EC	Eyes closed
ECS	Endocannabinoid system
EDSS	Expanded disability status scale
EMG	Electromyography
EO	Eyes open
ETA	Ethanolamine

FAAH	Fatty acid amid hydrolase
FSS	Functional Severity Scale
GABA	γ-Aminobutyric acid
GBP	Gabapentin
GI	Gastrointestinal
GPCR	G-protein coupled receptor
GPR18	G-protein coupled receptor 18
GPR55	G-protein coupled receptor 55
HC	Healthy control
HIV	Human immunodeficiency viruses
ITT	Intention-to-treat
LTD	Long term depression
LUTD	Lower urinary tract dysfunction
LUTS	Lower urinary tract symptoms
MAGL	Monoacylglycerol
MAS	Modified Ashworth scale
MS	Multiple sclerosis
MSFC	Multiple sclerosis functional composite
MSIS	Multiple sclerosis impact scale
MSQOL	Multiple sclerosis quality of life
MSS	Multiple sclerosis spasticity
NAM	Negative allosteric modulator
NAPE	N-Arachidonoyl phosphatidylethanolamine
NAPE-PLD	N-Acylphosphatidylethanolamine-hydrolyzing phospholipase D
NARCOMS	North American Research Committee on Multiple Sclerosis
NAT	N-Acetyltransferase
NMDA	N-Methyl-D-aspartate
NPP	Neuropathic pain
NRS	Numerical rating scale
OAB	Overactive bladder
OABSS	Overactive bladder symptom score
PASAT	Paced auditory serial addition test
PDQ	Perceived deficits questionnaire
PDQ	Perceived deficits questionnaire
PEA	Palmitoylethanolamide
P-gp	P-glycoprotein 1
PLC	Phospholipase C
PNS	Peripheral nervous system
PPARγ	Peroxisome proliferator-activated receptor gamma
PPMS	Primary progressive multiple sclerosis

PSS	Primary symptom score
RIS	Radiologically Isolated Syndrome
RCT	Randomised controlled trial
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SCID-IV	Structured clinical interview for diagnostics and statistical manual of mental disorders (DSM-IV) axis I disorders
SDMT	Symbol digit modality test
SNRI	Serotonin and norepinephrine reuptake inhibitors
SPMS	Secondary progressive multiple sclerosis
SRT	Spatial recall test
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
THC	Δ^9-Tetrahydrocannabinol
TMS	Transcranial magnetic stimulation
TRPV-1	Transient Receptor Potential Vanilloid 1
TSS	Tremor Severity Scale
TTF	Time to treatment failure
TUG	Timed up-and-go
UIE	Urinary incontinence episode
UK	United Kingdom
USA	United States of America
UTI	Urinary tract infection
UVR	Ultraviolet radiation
VAS	Visual analogue score

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INTRODUCTION

Multiple sclerosis (MS) is a neurodegenerative disease, and the most common cause of non-traumatic disability in young adults.[1] Although the underlying cause of MS is unclear, a combination of factors, including environmental exposure(s) and genetics, likely contribute to the development and progression of this disease.[2] Symptoms of MS are highly unpredictable, and often worsen as the disease progresses,[3] causing a decreased quality of life.[4–6] Currently, many symptomatic and disease-modifying therapies exist; however, many people with MS find these to be unsuccessful, and improved treatment options are still needed. *Cannabis* may have a potential role in mitigating MS symptoms. *Cannabis*-based medicines (CBMs) are available for MS, but more robust evidence is needed to determine the therapeutic value of CBMs. This systematic review aims to examine and critically appraise the current literature on CBM for the treatment and symptom management of MS.

CHAPTER 1: LITERATURE REVIEW

1.1 Multiple Sclerosis Disease Burden

Multiple sclerosis (MS) is a neurodegenerative disorder that generally presents early in adulthood. Most MS patients are typically diagnosed between ages 20 and 40 and MS is one of the main causes of non-traumatic disability in young adults.[1] The incidence of MS is higher in women, with 3 times more women having the disease than men.[7,8] In 2016, the global prevalence of MS was over 2 million, a 10.4% increase since 1990.[9] Regions with the highest MS prevalence include North America, Western Europe, and Australia.[9] In Canada, 77,000 adults (20 years and older) were living with MS in 2014/2015, equating to 1 per 358 Canadians.[7] While the incidence of MS in Canada remains relatively constant, prevalence is increasing,[10] likely due to increased survival times of those with MS.[8,10] The number of individuals in Canada living with MS is projected to increase to 133,635 cases by 2031.[11] This represents an important increase in disease burden within the Canadian population.

1.2 Multiple Sclerosis

Multiple sclerosis is a neurodegenerative autoimmune disease of the central nervous system (CNS) that causes degradation of myelin and CNS inflammation, as well as axonal degradation.[12] Myelin, the "white matter" of the brain and spinal cord, is a fatty layer that wraps around neurons to allow for fast, efficient nerve impulse transmission.[13] In MS, myelin is degraded resulting in an interruption in neuronal transmission and lesions in the brain and spinal cord.[13–15] These lesions account for the symptoms of MS.[14] A continued degradation and lack of myelin re-synthesis results in progression of the disease and worsening of symptoms.[3,16] Axonal loss also occurs in MS, either before or after immune destruction of myelin, and contributes to the symptoms and progression of the disease.[12]

1.2.1 Causes of Multiple Sclerosis

The underlying cause of MS is unknown.[17,18] It is generally accepted that MS is caused by a combination of environmental and genetic factors.[2,19] Globally, the lifetime risk of

developing MS is 1/330; this increases to 1/67 for children of those with MS, 1/37 for siblings of those with MS, and 1/5 for those with an identical twin with MS.[20] Additionally, age of MS onset is similar for monozygotic twins suggesting a genetic basis.[2] Regions farther from the equator, including Canada,[21] have a higher prevalence of MS.[2] This suggests environmental factors, such as lack of ultraviolet radiation (UVR) and Vitamin D, influence the development and progression of the disease.[19,22,23] Regardless of underlying cause, MS develops following an immune response that leads to neuronal cell death, demyelination, and neuronal dysfunction.[18,24] The possible immune pathways that cause MS are incompletely understood,[17] but immune B-cell activation of T-cells[25–27] and subsequent myelin degradation results in tissue damage and CNS lesions. This causes MS symptoms.[24]

1.2.2 Disease Course

Four main disease courses characterise MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS).[28] Clinically isolated syndrome (CIS) is defined as having a single "episode" of MS-like symptoms. When examined further (i.e. by MRI), evidence of abnormalities in the brain and/or spinal cord are usually found.[28] People who experience CIS may or may not develop MS in the future.[29] Relapsing-remitting MS (RRMS) is the most common type of MS, affecting approximately 85% of individuals.[30–32] With RRMS, the individual experiences relapses where symptoms present or worsen, followed by periods of remission or improvement.[3,28] These relapses are due to activation of immune cells in the CNS and inflammatory damage to neuronal myelin sheaths.[33] Approximately 80% of those with RRMS eventually develop SPMS.[30] SPMS is characterised by a steady progression of the disease with a decrease in distinct relapses, and is generally less inflammatory in nature than RRMS[28,34] Primary-progressive MS occurs in 10-15% of MS patients,[19] and is characterised by a continuous progression of the disease and disability from onset, with no relapses, and no periods of remission.[28] Finally, while not yet considered part of the main disease course of MS, radiologically isolated syndrome (RIS) occurs when MRI detects a lesion(s) suggestive of MS, yet there are no clinical symptoms.[31]

1.2.3 Diagnosis of Multiple Sclerosis

No solitary clinical feature or test can diagnose MS.[31] A diagnosis is often made after a thorough clinical history of past and current symptoms and typically requires an MRI.[32] The McDonald criteria, first established in 2001 and revised in 2005, 2011, and 2017,[35,36] is the current criteria for diagnosing MS. According to these criteria, the diagnosis of MS requires dissemination is space with at least two distinct lesions anatomically located in the central nervous system over time.[19,35–37] Dissemination in space and time may be satisfied by clinical and/or MRI criteria.[19,35,36] Presence of cerebrospinal fluid (CSF)-specific oligoclonal bands may also demonstrate dissemination in time.[36] Evoked potential studies may find lesions that are clinically silent, but these are not commonly used in diagnostic work-ups.[19]

1.2.4 Multiple Sclerosis Symptoms and Assessment Measures

The symptoms of MS are highly variable and unpredictable and depend on the affected region of the CNS.[38] Symptoms include balance problems and dizziness, bladder and bowel dysfunction, cognitive impairment (especially processing speed and short-term memory), depression, fatigue, difficulty with mobility or gait, optic neuritis, pain, numbness/tingling, sexual dysfunction, spasticity, tremor, heat intolerance (Uhthoff's Phenomenon), weakness, and impaired coordination.[38,39] Among the most common symptoms are fatigue, pain, and cognitive changes, affecting 90%, 50%, and 40-70% of those with MS, respectively.[38]

Different assessment measures are available to quantify the severity of MS symptoms and to assess the impact of symptoms on a person's function. These assessment measures have variable use with some being more widely used/recognised than others. The assessment measures are either self-reported or assessor-reported tools (Table 1.1). A Multiple Sclerosis Task Force, associated with the Academy of Neurologic Physical Therapy, reviewed 63 measures of MS symptoms and 10 were deemed "highly recommended" (marked in Table 1.1) due to their psychometric properties, clinical utility, or both.[40,41]

Table 1.1. Assessment measures for multiple sclerosis symptoms

Name of outcome	Description of outcome	Patient-reported outcome
Spasticity		
Ashworth and Modified Ashworth Spasticity Scale	Assesses muscle tone as follows: 0, normal tone; 1, slight increase in muscle tone, "catch" and release, or minimal resistance at the end of the range of motion when limb is moved in flexion or extension; 2, more muscle tone through range of motion, but limbs still easily moved; 3, substantial increase in muscle tone; 4, rigid limb in extension or flexion.[42] The MAS also has 1+ between scores 1 and 2, to indicate a slight increase in muscle tone, "catch", and minimal resistance throughout the remainder (less than half) of the range of motion.[42]	No
NRS	Subjects report their level of spasticity from 0 (no spasticity) to 10 (worst possible spasticity).[43]	Yes
H/M ratio	The ratio between the maximum H reflex and maximum M response to measure the level of spasticity.[44] The H reflex is usually increased with spasticity while the M response, the maximum response of a muscle when the motor nerve is directly stimulated, is not.[44] The H/M ratio is calculated using nerve conduction study techniques.[44] For the H reflex, the sensory fibers are stimulated directly, they travel to the spinal cord where they synapse and then stimulate the motor nerve creating a delayed sub-maximal motor response.[44]	No
TTF	This measure is defined as termination of treatment (withdrawal) before Visit 3, or worsening spasticity (increase in NRS score), or increase in, or addition of, anti-spasticity or disease modifying medication.[45]	No
Stretch Reflex	A neurophysiological measure that is exaggerated in MS and can be recorded via electromyography (EMG) to quantitatively assess spasticity in major joints (wrist, knee, elbow and ankle). During the procedure, the evaluator repeatedly moves the distal segment of the joint over the range of motion in order to obtain EMG recordings of elongation of the spastic muscle.[46,47]	No
Discontinuation of Treatment	The reasons for discontinuing treatment (adverse events, inefficacy, etc.) are described.[48]	Yes
Spasticity Score	Physician rates deep tendon reflexes, resistance to leg stretches, and abnormal reflexes on a scale of 0 (absent) to 4 (abnormally increased) and calculates the total of these scores and divides it by the number of observations.[49]	No
Effectiveness of Treatment	Assesses efficacy of treatment spasticity as follows: greatly improved, slightly improved, no effect, slightly worse or much worse.[50]	Yes
Effectiveness of Treatment	A dichotomous (yes/no) answer was given for 'response' based on the prescribing doctor's analysis and the overall impression of the patient's response to treatment.[51]	No
Bladder Dysfunction		
OABSS	Seven-item questionnaire assessing overactive bladder symptoms (i.e. daytime frequency, nighttime frequency, urgency, incontinence).[52,53] The score range is between 0-28,[53] with moderate to severe being at least 6 points on the OABSS.[54]	Yes
Functional Bladder Capacity	Subjects record voided (plus catheterised where applicable) urine volumes in a diary 3 days per week.[55]	Yes
Incontinence Episodes	Subjects complete a diary recording the frequency of incontinence episodes.[56,57]	Yes
Cognition		

Table 1.1. Assessment measures for multiple sclerosis symptoms

Name of outcome	Description of outcome	Patient-reported outcome
PASAT	Assesses auditory information and processing speed, as well as calculation ability[58] in which the subject is presented with a number every 3 seconds, and the subject must add the new digit to the one before it.[59] Part of the MSFC.[59]	No
10/36 SRT	Measure of visuospatial memory[60] in which 10 pieces are placed on a checker-board. For three trials, participants look at the board for 10 seconds. The participant then needs to replicate the pattern on another board. After 20-25 minutes, the participants are asked to replicate the design again on another board.[61]	No
Tremor		
Tremor Index	Postural tremor (scored in outstretched and batwing positions) and intention tremor severity were scored individually (0-10) in each arm and then added to get the total score (0-60).[62,63]	No
9-HPT[a]	A motor task in which the subject picks up nine pegs one at a time and as quickly as possible puts them in nine holes. Once they are in the holes, the subject removes them again as quickly as possible, one at a time. The time to complete the task is the score. Two trials with the dominant hand are followed by two trials with the non-dominant hand.[64] Part of the MSFC.[59]	No
Disability Progression		
EDSS	10-point scale, with 0.5 point increments, to quantify MS disability.[65] A score of 1 to 4.5 indicate someone with MS who is able to walk without any aid. A score of 5 to 9.5 indicate an impairment in walking.[65]	No
MSFC[a]	1) Timed 25-Foot walk; 2) 9-Hole Peg Test (9-HPT); and 3) Paced Auditory Serial Addition Test.[59]	No
Dizziness Handicap Inventory[a]	25-item questionnaire measuring a person's perception of disability and handicap (either "always" (4 points), "sometimes" (2 points) or "never" (0 points)) in three areas: physical, emotional, functional. The higher the total score (out of a possible 100), the worse the handicap.[59,66]	Yes
Pain		
NRS	Self-reported pain scale in which the subject rates their pain from 0 (no pain) to 10 (worst pain imaginable).[67]	Yes
VAS	This scale uses a 100 mm straight line with "no pain at all" (0 mm) on one side and "pain as bad as it could be" (100 mm) on the other.[68,69] The subject then marks their pain on the line, indicating their level of pain.[68,69]	Yes
CRS	The CRS is an 11-point rating scale (0 to 10) to evaluate the subjects' perceived change in muscle stiffness, with 0 being very much better and 10 being very much worse;[70] a score of 0-3 is considered "relief of muscle stiffness".[70]	Yes
Balance/Walking		
Timed 25-foot walk[a]	The subject, starting in a standing and upright position, is instructed to walk 25 feet in a straight line as fast and safely as possible. The subject is able to use an assistive device. The time to perform the walk twice is measured and the average of two successful trials is recorded as the score.[71] Part of the MSFC.[59]	No
Berg balance scale[a]	This scale consists of 14 functional balance tasks of increasing difficulty performed by the participant and rated by the assessor. A four-point scoring scale is used, with a total score between 0 and 56; higher scores mean better balance.[72]	No
Ambulation Index	The AI is a rating scale that assesses mobility based on time and degree of assistance required when walking 25 feet as quickly as possible but safely. The AI	No

Table 1.1. Assessment measures for multiple sclerosis symptoms

Name of outcome	Description of outcome	Patient-reported outcome
	is scored on a 10-point scale with anchors of asymptomatic and fully active (0) through bedridden (10).[71]	
Postural Sway	Measure of dynamic posturography in which a subject stands on a force plate and is led through a series of conditions (eyes open, eyes closed, etc.) in order to assess the subject's balance.[73,74]	No
12-item MS walking scale[a]	A 12-item scale where subjects rank each item from 1 (not at all) to 5 (extremely). There is a total score of 60, with a higher score meaning more impairment.[75]	Yes
6-minute walk test[a]	Patients were instructed to walk at a quick yet comfortable pace back and forth along a pre-measured walkway for 6 minutes. At the end of 6 minutes, the total distance walked is calculated.[76]	No
TUG with Cognitive Manual[a]	Measure of dynamic balance. The subject stands from a chair and walks 3 m, then walks back to the chair and sits down. The time is from when the pelvis lifts off the chair to when it reaches the chair again. For cognitive portion, the subject has to subtract 3 from a number between 20-100 while preforming the task.[59]	No
Walking Speed	Measure of walking ability in which subjects walk barefoot at a self-selected speed on a 10 m walkway at least six times, and the speed is recoreded[77]	No
Quality of Life		
MSQOL-54[a]	Self-reported 54-item scale assessing subjects' overall perception of quality of life. There are 2 subscales along with two summary scores, and two additional single-item measures, all with their own rating measures. This scale touches on physical function, pain, emotional well-being, energy, social functions, cognitive function, overall quality of life, and sexual function.[78]	Yes
MSIS-29[a]	This self-reported assessment measures the psychological and physical effect of MS.[79] It is a 29-item questionnaire where subjects assess items relating to physical and mental health and wellbeing over the past two weeks. Items are ranked from 1 (not at all) to 5 (extremely).[80]	Yes
SCID-IV	Interview to creates a list of current and lifetime DSM-IV diagnoses of the subject.[81]	No
General Symptoms		
Primary Symptom Score	The Visual Analogue Scale (VAS) score for the subject's chosen symptom.[82]	Yes

9-HPT: 9-hole peg test; 10/36 SRT: 10/36 spatial recall test; AI: ambulation index; CRS: category rating scale; DSM: diagnostic and statistical manual of mental disorders; EDSS: expanded disability status scale; MSFC: multiple sclerosis functional composite; MSIS: multiple sclerosis impact scale; MSQOL: multiple sclerosis quality of life; NRS: numerical rating scale; OABSS: overactive bladder symptom score; PASAT: paced auditory serial addition test; PDQ: perceived deficits questionnaire; SDMT: symbol digit modality test; SCID-IV: structured clinical interview for diagnostics and statistical manual of mental disorders (DSM-IV) axis I disorders; TTF: time to treatment failure; TUG: timed up-and-go; VAS: visual analogue scale;

[a]=highly recommended measures[40]

1.2.5 Treatment for Multiple Sclerosis

As there is no cure for MS, current therapies aim to treat acute relapses, decrease or slow disease progression, or treat symptoms associated with MS.[14,39,83] Treatment of acute relapses may involved the use of high dose corticosteroids (IV methylprednisolone or high dose oral prednisone), and adrenocorticotropin hormone (ACTH).[84,85] These therapies have anti-inflammatory and immunosuppressive properties[86] and target active immune cells and inflammation present during a relapse.[33] For disease progression, disease-modifying therapies (DMTs) are available,[87] which reduce relapses and the number of new lesions seen on imaging in clinical trials.[88–90] Debate exists, though, as to their effectiveness on disability outcomes long-term.[91] DMTs are effective for relapsing forms of MS, as they target active inflammatory disease,[87,92,93] however they are less efficacious once degeneration begins.[1] Over a dozen treatments are available for relapsing remitting MS,[94] but only one disease modifying therapy, ocrelizumab, is currently approved for PPMS.[95] The reduced effectiveness of DMT's in PPMS may be explained by fewer active plaques and inflammation in progressive MS.[34] In Canada, first-line treatments for MS include the beta-interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, and ocrelizumab,[88,92,95,96] while second-line treatment options include fingolimod, natalizumab, alemtuzumab, and cladribine.[88,92,96] For symptomatic treatment, a large number of drug therapies are available (Table 1.2), particularly for bladder, spasticity, and pain,[14,39,97] however these options are not without side effects.[14,98–101] There are also limited options for MS fatigue and cognitive dysfunction,[14,39,97,101] and off-label use of drugs for both disease progression[102] and symptom management is not uncommon.[14,39,97,101] This highlights the need for better MS medications despite the large number being currently available.

Table 1.2. Symptomatic therapy used for various symptoms of multiple sclerosis in Canada.[14,39,97]

Symptom	Treatment Options
Spasticity	• muscle relaxant: baclofen • alpha-2 adrenergic agonists: tizanidine • benzodiazepines: diazepam, lorazepam
Pendular Nystagmus	• NMDA receptor antagonist: memantine • anti-convulsant: gabapentin • corticosteroid: methylprednisone (IV), prednisone (oral)
Pain	• anti-convulsant: gabapentin, pregabalin, carbamazepine**,** phenytoin • TCAs: amitriptyline, nortriptyline • benzodiazepines: lorazepam • muscle relaxant: cyclobenzaprine, baclofen, methocarbamol • narcotic analgesic: acetaminophen-oxycodone
Heat Sensitivity	• potassium channel blocker: fampridine SR
Bladder /LUTS	• botulinum A toxin • anticholinergics: oxybutynin, darifenacin, solifenacin succinate, flavoxate • anti-diuretic: desmopressin • alpha-1 blockers: prazosin, tamsulosin, darifenacin • beta-3 adrenergic agonists: mirabegron • TCAs: imipramine
Gait	• potassium channel blocker: fampridine SR
Fatigue	• CNS stimulant: methylphenidate, amantadine, modafinil
Tremor	• anticonvulsants: gabapentin, levetiracetam, topiramate, primidone • beta-blockers: propranolol • antibiotic: isoniazid
Sexual dysfunction	• erectile dysfunction: sildenafil nitrate, alprostadil, papaverine, tadalafil, vardenafil • anti-convulsant: carbamazepine, phenytoin
Bowel Dysfunction	• stool softener: docusate oral • laxative: bisacodyl, sodium phosphate, psyllium hydrophilic mucilloid, magnesium hydroxide
Cognitive Dysfunction	• amphetamines • acetylcholinesterase inhibitors: donepezil
Depression	• SSRIs: sertraline, citalopram, fluoxetine, paroxetine • TCAs: amitriptyline, nortriptyline • SNRIs: mirtazapine, venlafaxine, desvenlafaxine

CNS: central nervous system; LUTS: lower urinary tract symptoms; NMDA: N-Methyl-D-aspartic acid; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor TCA: tricyclic antidepressant

1.2.5.1 Complementary and Alternative Medicine

Individuals living with MS often try complementary and alternative medicine (CAM) acupuncture, aromatherapy, Ayurveda, chiropractor, electromagnetic therapy, homeopathy, hypnosis, massage, naturopathy, and Reiki.[103] Furthermore, some turn to self-medication with herbal supplements and/or *Cannabis*.[103–105] The North American Research Committee on

Multiple Sclerosis (NARCOMS) registry evaluated *Cannabis* use in MS and found that 47% of 5481 survey respondents considered *Cannabis* a possible option to treat the symptoms of MS.[106] Currently, a limited evidence-base exists for *Cannabis* and *Cannabis*-based medicine (CBM) use in MS. Therefore, future studies evaluating *Cannabis* and CBM should focus on which MS symptoms are best treated with CBM, which cannabinoid(s) is most beneficial for specific MS symptoms, the best route of administration (oral, oromucosal, inhalation), the negative effects of CBM and if they subside with prolonged use, and possible interactions between CBM and other MS medications.[107]

1.3 Endocannabinoid System

The endocannabinoid system works throughout the body and is very prevalent in the CNS, as a synaptic regulator,[108] and in immune microglial cells.[109] The endocannabinoid system has three elements: various receptors; the endogenous cannabinoids that act on these receptors; and the enzymes that synthesise and breakdown endocannabinoids.[110] The synthesis and subsequent activity of endocannabinoids with cannabinoid receptors modulate neurotransmitter release.

1.3.1 Receptors of the Endocannabinoid System

The cannabinoid receptors are rhodopsin-like G-protein coupled receptors (GPCRs),[111,112] which are located throughout the body (Figure 1.1).[113] Both exogenous and endogenous cannabinoids interact with these receptors causing an inhibition in neurotransmitter release.[114,115] Cannabinoids also interact with other receptors, including transient receptor potential vanilloid type-1 (TRPV1) and the GPCR, GPR55.[116] The actions of cannabinoids result in various pharmacological effects, some of which may be beneficial for the treatment of many different conditions.

CB1 receptors are the most abundant GPCR in the CNS with high expression in both the brain and spinal cord.[117] In the brain, CB1 is highly expressed in the hippocampus, cortex, cerebellum, and basal ganglia, brain areas associated with memory and motor control.[118,119] CB1 is expressed in the pain pathways of both the brain and spinal cord,[119,120] making these receptors

a useful option for pain therapies. CB1 receptors present on microglial cells are involved in immune mediation.[121]

CB2 receptors are peripherally located on immune cells, including B- and T-cells and monocytes, as well as in immune tissues, such as the spleen and tonsils.[122] This receptor is also expressed in the brain and spinal cord, but to a limited degree.[118,123] CB2 receptors may be a target for various immune responses and, therefore, can be useful in neuropathies that involve excessive inflammation.[124] CB2 receptor upregulation may occur in the CNS during inflammation with expression mainly in microglia, the macrophages of the CNS.[124] Therefore, CB2 receptor activation can lead to protection against neuroinflammation.

Cannabinoids can interact with other receptors in addition to CB1 and CB2 receptors. These include the transient receptor potential vanilloid type-1 (TRPV1) and the GPCR, GPR55.[116] Both are located in the CNS, [125–128] with TRPV1 also involved in pain management.[128] Endocannabinoids do not activate GPCR GPR18, which is also abundant in the CNS and microglial cells;[129–131] however, exogenous cannabinoids interact with this receptor.[116]

1.3.2 Endogenous Cannabinoids

Anandamide (AEA) and 2-arachidonylglycerol (2-AG) are the two principal endocannabinoids that act on cannabinoid receptors. The synthesis of AEA and 2-AG, from precursors located in the cell membrane,[132] is mediated by N-acetylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) and diacylglycerol lipase (DAGL), respectively.[114,115] Through the interaction with cannabinoid receptors, endocannabinoids are able to inhibit neurotransmitter release and neuronal signalling.[114] AEA is a partial agonist of the CB1 receptor, while 2-AG is a full agonist of both the CB1 and CB2 receptors.[114,133,134] After interaction with cannabinoid receptors, AEA is degraded by fatty acid amide hydrolase (FAAH) into arachidonic acid (AA) and ethanolamine, while 2-AG is degraded by monoacylglycerol lipase (MAGL) into arachidonic acid and glycerol (Figure 1.2).[114,115]

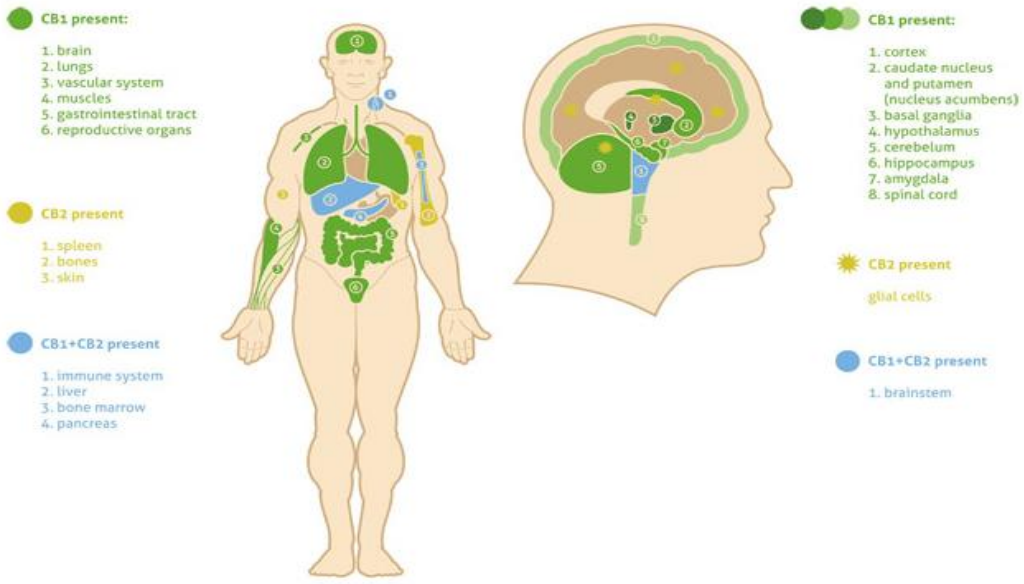

Figure 1.1. Location of CB1 and CB2 receptors in the body. Locations of CB1 receptors are in green, location of CB2 receptors are in yellow, and locations with both CB1 and CB2 receptors are in blue.

Location of CB1 and CB2 receptors around the body from © Fundación CANNA. (n.d.). The Endocannabinoid System. Fundación CANNA. Retrieved from https://www.fundacion-canna.es/en/endocannabinoid-system. By permission from author.

1.3.3 Mechanism of Action of Endocannabinoids

The endocannabinoids, AEA and 2-AG,[111] are retrograde synaptic messengers with a complex mechanism of action. AEA and 2-AG interaction with pre-synaptic CB1 receptors results in inhibition of pre-synaptic activity.[119] The CB1 receptor suppresses neurotransmitter release in two ways: inhibition of voltage-gated Ca^{2+} channels on the presynaptic cell and induction of long-term depression (LTD).[114,115] With post-synaptic depolarization, voltage-gated Ca^{2+} channels open increasing intracellular calcium,[132,135] which subsequently activates N-acetyltransferase (NAT) and phospholipase C (PLC).[132,135] The activation of NAT converts phosphatidylethanolamine (PE) to N-arachidonoyl phosphatidylethanolamine (NAPE).[132,135] NAPE is metabolized to AEA through the activity of NAPE-PLD.[132,135] Similarly, the activation of PLC converts phosphatidylinositol (PI) to diacylglycerol (DAG),[135] and DAG is subsequently

converted to 2-AG by DAG lipase (DAGL) .[135] mGluR1/5 activation in the post-synaptic neuron can also cause activation of PLC, resulting in synthesis of DAG. DAG is then cleaved by DAGL resulting in 2-AG synthesis.[119,136] The newly synthesised endocannabinoids then leave the post-synaptic cell and move in a retrograde manner to activate CB1 receptors on the pre-synaptic cell.[119,136] The binding of cannabinoids to CB1 on the pre-synaptic cell leads to G-protein activation, and the subsequent dissociation of the $G_{\beta\gamma}$ and $G\alpha_i$ subunits. The $G_{\beta\gamma}$ subunit causes inwardly-rectifying K^+ channels to open,[135,137] allowing K^+ to enter the presynaptic cell. It also causes Ca^{2+} channels to close, inhibiting the influx of Ca^{2+} into the pre-synaptic cell.[119,136] The influx of K^+ and inhibition of influx of Ca^{2+} results in hyperpolarization of the pre-synaptic cell. This hyperpolarization prevents release of neurotransmitters.[119,136] $G\alpha_i$ subunit activation inhibits the adenylyl cyclase-phosphokinase A (AC-PKA) pathway, therefore decreasing the formation of cyclic AMP (cAMP), resulting in LTD.[108,137]

Once synthesized, AEA and 2-AG may enter the post- or pre-synaptic neuron, respectively, and undergo inactivation by enzymatic hydrolysis.[110,135] The two major endocannabinoid-metabolizing enzymes are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which catabolize AEA and 2-AG, respectively.[132] The amide bond of anandamide is hydrolyzed in the post-synaptic cell by FAAH to yield arachidonic acid (AA) and ethanolamine (ETA).[110,132] The ester bond of 2-AG is hydrolyzed in the pre-synaptic cell by MAGL to yield arachidonic acid (AA) and glycerol.[110,132] The products of the catalysis are then recycled into phospholipids that can integrate into the cell membrane.[132]

Since the discovery of endocannabinoids and their mechanism of action, it has been thought that this system can be exploited by synthetic and exogenous cannabinoids for therapeutic uses. Cannabinoid use for the treatment of neurological disorders is increasing and show promise for epilepsy, neuropathic pain, and MS.[138–140] Additionally, their presence on immune cells suggest their involvement in inflammation and immune mediation and, hence, possible therapeutic targets in many autoimmune disorders such as Crohn's disease and arthritis.[141]

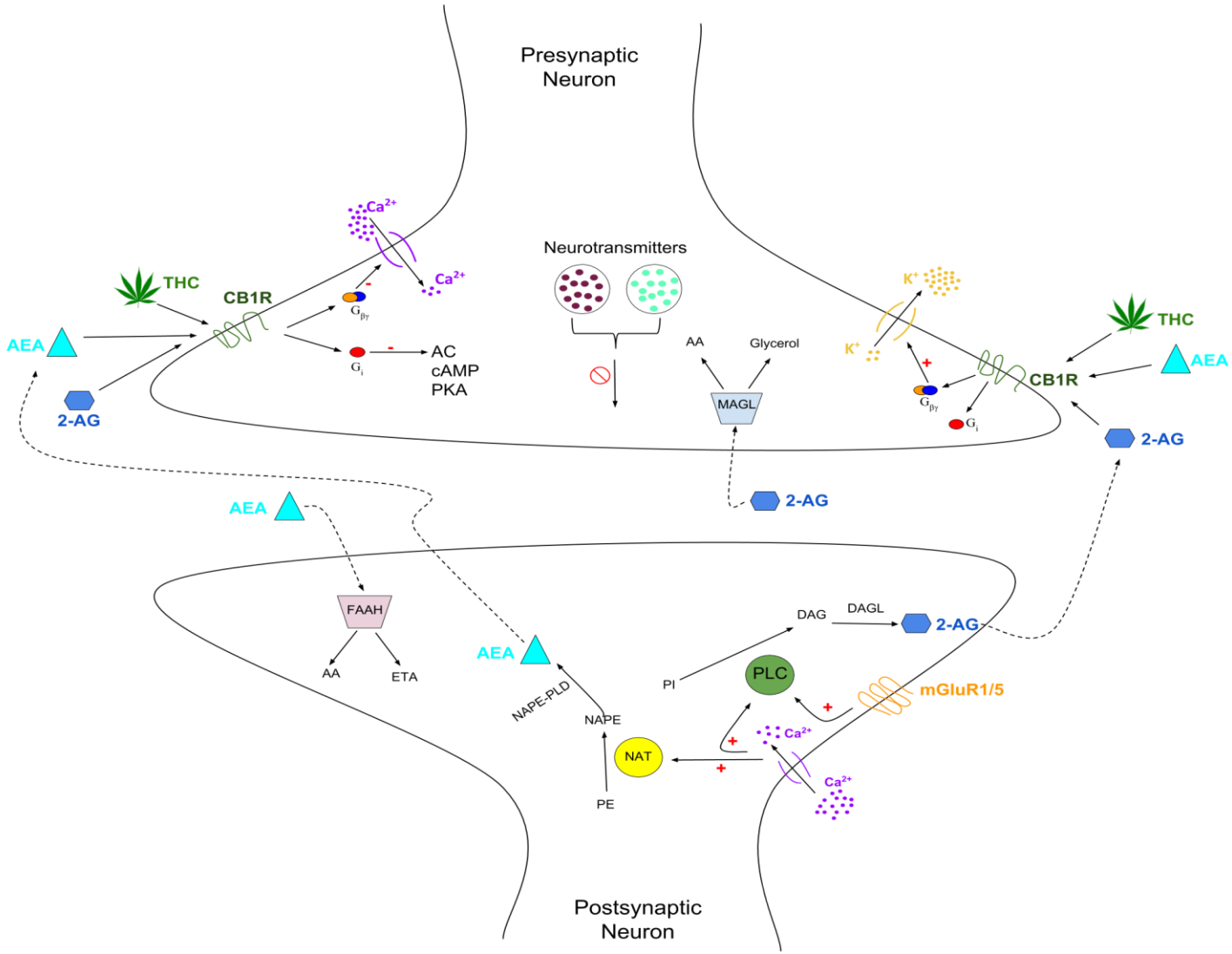

Figure 1.2. Mechanism of action of cannabinoids at the CB1 receptor, causing inhibition of calcium (Ca^{2+}) channels and activation of inwardly-rectifying potassium (K^{+}) channels, leading to inhibition of neurotransmitter release.

1.4 Cannabinoids and MS

Cannabinoid receptor presence in the CNS allows cannabinoids to inhibit neurotransmitter release, ameliorating MS symptoms. Nerve impulse transmission results in the release of the presynaptic excitatory neurotransmitter, glutamate,[142] which subsequently crosses the synapse and binds to ionotropic glutamate receptors in the synaptic cleft.[142] Glutamate receptor binding leads to an ionic flux of calcium that induces the potentiation of a nerve impulse down the neuron.[142] In normal conditions (Figure 1.3A), both movement and sensation are controlled by the nervous system balancing excitatory and inhibitory signals. In disease states such as MS (Figure 1.3B), the damage to the nervous system, due to the loss of myelin, causes an increase in glutamate release, which leads to an excess of excitation and neurotransmitter signalling.[142,143] This results in the symptoms associated with MS.[142,143] Invading immune cells and glial cells can increase this glutamate release, leading to more excitation.[142,144,145] Moreover, GABAergic inhibitory nerves are lost in MS, leading to a loss of ability to counteract the excessive excitation.[142,143] Excessive glutamate excitotoxicity can lead to metabolic failure and subsequent accumulation of calcium with further nerve loss and greater disability.[142,146,147] Cannabinoids acting on the CB1 receptor can limit excitotoxicity and slow nerve loss, therefore theoretically controlling symptoms associated with MS (Figure 1.3C).[142,143,148]

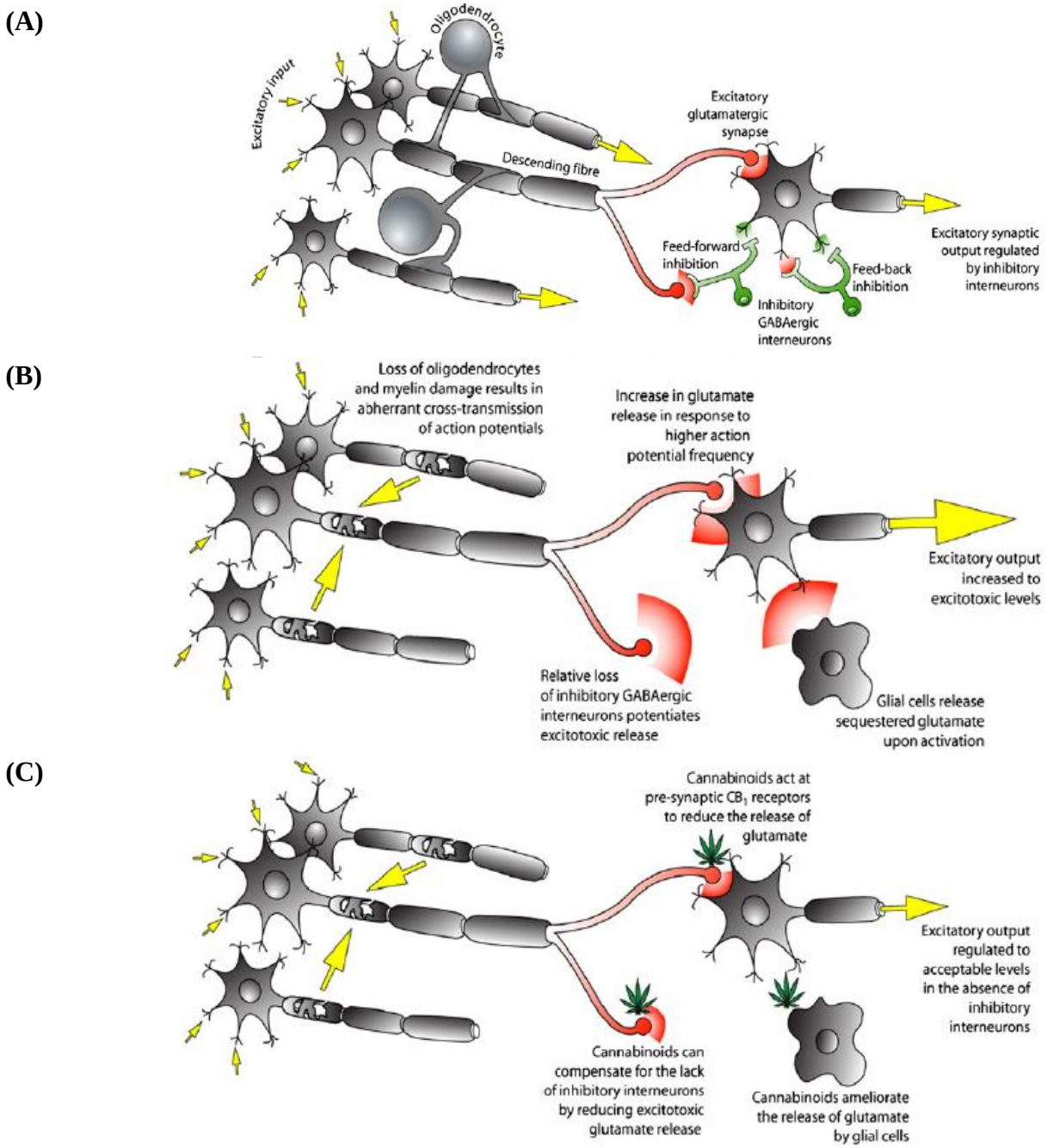

Figure 1.3. Neurotransmission of neuronal impulses in normal conditions (A), MS disease state (B), and MS disease state with the use of cannabinoids acting on CB1 receptors (C).

Neurotransmission under normal conditions (A), during MS disease progression (B), and subsequent cannabinoid control of neurotransmission in disease states (C) from © Baker, D., Pryce, G., Jackson, S. J., Bolton, C., & Giovannoni, G. (2012). The biology that underpins the therapeutic potential of cannabis-based medicines for the control of spasticity in multiple sclerosis. *Multiple Sclerosis and Related Disorders, 1*(2), 64-75. Elsevier. By permission from publisher.

In immune-mediated demyelinating conditions, such as MS, activation of CB2 receptors can, in theory, decrease the harmful inflammatory response that causes the death of both young oligodendrocyte precursor cells as well as mature oligodendrocytes to enhance cell survival.[149] Moreover, CB2 receptor agonism may not only stop demyelination, but may promote the repair of damaged axons.[149] Therefore, CB2 receptors could be involved in both the protection and recovery of myelin in MS (Figure 1.4).[149]

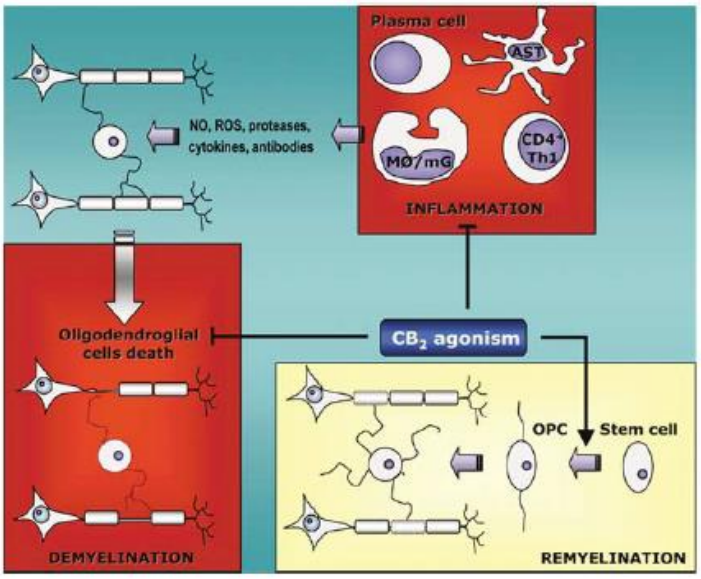

Figure 1.4. CB2 receptor agonism as a mechanism of neuroprotection and remyelination in MS.

CB2 receptor agonism as a mechanism of neuroprotection and remyelination from © Arévalo-Martín, A., García-Ovejero, D., Gómez, O., Rubio-Araiz, A., Navarro-Galve, B., Guaza, C., … Molina-Holgado, F. (2008). CB2 cannabinoid receptors as an emerging target for demyelinating diseases: from neuroimmune interactions to cell replacement strategies. *British Journal of Pharmacology*, *153*(2), 216–25. https://doi.org/10.1038/sj.bjp.0707466. By permission from publisher.

Much anecdotal evidence is present to suggest that CBM can alleviate symptoms associated with MS. This evidence, in combination with the known cannabinoid receptor presence throughout the body and involvement in immune mediation, underlines the basis that CBM may improve some MS symptoms, and potentially slow disease progression.

1.5 Phytocannabinoids

Phytocannabinoids are found in the *Cannabis* plant, *Cannabis sativa,* and interact with the endocannabinoid system. This plant contains over 140 different cannabinoids, with the most prominent ones being Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD),[150,151] as well as other bioactive molecules known as terpenes.[152,153]

1.5.1 Δ-9-Tetrahydrocannabinol

THC, the main psychoactive component of *Cannabis*, is responsible for the signature "high" of marijuana, with side effects including sedation and intoxication.[154] THC is a partial agonist of both CB1 and CB2 receptors,[155] and its action at the CB1 receptor is responsible for its regulation of synaptic transmission[142,143] and psychoactive effects.[137] THC also has immunosuppressive properties.[154] The actions of THC at the CB1 receptor, and with the immune system, make it a strong candidate for MS patients.

1.5.2 Cannabidiol

CBD, the other main cannabinoid present in cannabis, is non-intoxicating. CBD does not bind to either CB receptor, but it is a negative allosteric modulator (NAM) of the CB1 receptor.[155] It may act as a neuromodulator,[156] as well as have anti-inflammatory and immunosuppressive properties such as inhibiting pro-inflammatory cytokines and activating anti-inflammatory pathways in microglial cells.[157] Therefore, CBD is thought to be especially useful candidate in ameliorating the progression of autoimmune disorders, including MS. Additionally, CBD can antagonise the adverse effects of THC, such as intoxication and sedation, while also having its own therapeutic effect.[142,154,158] This suggests value in the co-administration of THC and CBD for therapeutic use.

1.5.3 Δ-9-Tetrahydrocannabinol/Cannabidiol Interaction

Interactions between CBD and THC produce either enhancing, opposing, or neutral effects. These variations in effects are due to differences in dosing, ratios of THC to CBD, routes of administration, order of dose (CBD administration either before or simultaneously to THC), and differences in treatment duration (chronic vs. acute).[137,159] Both pharmacokinetic (kinetic) and pharmacodynamic (dynamic) mechanisms control the interactions between CBD and THC.[137] CBD potentiates the effects of THC (via a kinetic mechanism).[137,160,161] CBD hinders THC metabolism, heightening the effects of THC.[159,162] Conversely, simultaneous co-administration of CBD and THC may result in attenuation of some effects of THC (via a dynamic mechanism).[137,160,161,163] CBD is a negative allosteric modulator of the CB1 receptor,[155] causing it to reduce the potency and efficacy of THC.[164]

1.5.4 The Entourage Effect

In addition to the cannabinoids CBD and THC, phytocannabinoids such as tetrahydrocannabivarin, cannabigerol, and cannabichromene, are also present in *Cannabis*,[153] as are organic compounds known as terpenes.[152,153] Terpenes and phytocannabinoids share a precursor molecule,[153,165] and these terpenes can result in phytocannabinoid-terpene interactions and synergism.[153] The interaction of these molecules results in the entourage effect, an increase in therapeutic efficacy,[153] due to an alteration of pharmacokinetic and pharmacodynamic properties.

1.5.5 Pharmacodynamics of Phytocannabinoids

The pharmacodynamic properties of *Cannabis* is based on the effects of the most prominent cannabinoids, THC and CBD. These phytocannabinoids are highly promiscuous and interact with many receptors beyond CB1 and CB2 (Table 1.3). THC activation of the CB1 receptor results in inhibition of neurotransmitter release, via the same mechanism as endogenous cannabinoids (Figure 1.2). CBD also antagonises CB1 and CB2 agonists,[166,167] which explains CBD's ability to attenuate the side effects caused by THC.[137,160,161] Additionally, activation of the CB1 receptor can inhibit the release of many neurotransmitters at both excitatory and

inhibitory synapses, including 5HT, glutamate, GABA, D-aspartate, dopamine, acetylcholine and noradrenaline, with both short and long-term effects.[137]

Table 1.3. THC and CBD actions on various receptors

Receptor	THC	CBD
CB1	Weak partial agonist[155]	Negative allosteric modulator[155]
CB2	Weak partial agonist[155]	Inverse agonist[158,166,167]
GPR55/GPR18	Agonist[168]	Antagonist[165]
$5HT_{1A}$	Agonist[169]	Agonist[170]
μ/σ opioid receptors	Positive allosteric modulator[171]	Positive allosteric modulator[171]
PPARγ	Agonist[172,173]	Agonist[174]
TRPV1	No effect[175]	Agonist[165,174]
D2High	Conflicting evidence[176]	Partial agonist[177]

$5HT_{1A}$: serotonin 1A receptor; CB1: cannabinoid receptor 1; CB2: cannabinoid receptor 2; CBD: cannabidiol; D2High: dopamine D2 high receptors; GPR55: G-protein coupled receptor 55; GPR18: G-protein coupled receptor 18; PPARγ: peroxisome proliferator-activated receptor gamma; THC: Δ-9-tetrahydrocannabinol; TRPV1: transient receptor potential cation channel subfamily V member 1

1.5.6 Pharmacokinetics of Phytocannabinoids

Route of administration is important when determining the effects of CBM. CBM can be administered via smoking/vaporization, orally, oromucosally, and less commonly, topically[137,178] and each route has different onsets and duration of action.[155] Furthermore, administration of cannabinoid products results in large inter-individual differences in peak plasma concentrations and peak effects.[137] Smoking/vaporization of *Cannabis* results in high bioavailability of cannabinoids, averaging about 30% for both THC[179] and CBD.[180] Onset of effect is rapid, usually within 5-10 minutes, with a dose-related duration between two and four hours.[155] Although absorption by inhalation is rapid, it is highly variable and depends on depth of inhalation, puff duration, and breath hold.[137] Oral ingestion of cannabinoids induces a slower onset of action (60-180 minutes), lower peak blood levels, and longer duration of effects compared to smoking (six to eight hours).[137,155] With oral administration, first pass metabolism results in low bioavailability of both THC and CBD, ranging between 4-20% and 13-19% for THC[178] and CBD,[181] respectively. Oromucosal administration has an onset of effect of 15-45 minutes with a duration of 6-8 hours.[155] Finally, topical administration of cannabinoids poses a problem, as cannabinoids are hydrophobic, so transport across the aqueous layer of skin is the rate-limiting step.[137,178]

The cannabinoids undergo delayed distribution after systemic absorption.[137,178,182] THC and CBD are both lipophilic and are taken up by fatty tissue and highly perfused organs such as the brain, heart, and liver.[137,174,178] THC and CBD are highly protein bound, to both albumin and lipoproteins,[178] with an unbound fraction of 1 – 5%.[174,178] The blood-brain barrier (BBB) limits THC's ability to access the brain, contributing to a delay in psychoactive effects compared to peak plasma concentrations.[137,183] The efflux transporter P-glycoprotein (P-gp) mediates THC's movement across the BBB, and limits the accumulation of THC in the brain.[184–186] Conversely, CBD is not a substrate of P-gp, and therefore its accumulation in the brain is independent of these transporters.[187] However, CBD inhibits P-gp,[188] resulting in higher brain concentrations of THC with co-administration of the two cannabinoids.[188]

Cannabinoid elimination occurs mainly by hepatic cytochrome P450 (CYP) enzyme-mediated metabolism. THC is metabolized by CYP2C9/19, and CYP3A4,[178] and CBD is hydroxylated by CYP3A4 and CYP2C8/9/19.[174] Initial metabolites of THC are 11-hydroxy-THC (active) and 11-nor-9-carboxy-THC (inactive),[137,178] while CBD is hydroxylated to 7-hydroxy-CBD (active) and 6-hydroxy-CBD.[174] Oral administration results in a greater metabolism of THC to 11-hydroxy-THC, therefore causing similar plasma concentrations of THC and the active hydroxy metabolite.[137,178,189] Via inhalation, plasma values of 11-hydroxy-THC appear rapidly and peak shortly after THC administration (about 15 minutes after the start of smoking).[137,178] CBD also inhibits the formation of THC metabolites catalyzed by CYP3A4, with minimal effect on CYP2C9,[190] subsequently causing a decrease in the formation of 11-hydroxy-THC.[137,191,192]

Excretion of THC metabolites occurs via feces and urine, with 80-90% being excreted as the metabolite, 11-nor-9-carboxy-THC.[178] THC metabolites from a single dose can be detected in plasma for up to 13 days in chronic smokers (terminal elimination half-life of 12.6 days),[137,178,193,194] and low levels of THC metabolites have been detected after more than 5 weeks in urine and feces of cannabis users.[137,190] This is likely due to the extensive accumulation and release of THC from body fat.[137,194] The half-life of CBD is 1-2 days,[174,195] with CBD metabolites excreted mainly in the feces,[174] as hydroxylated derivatives of CBD-7-oic acid, or as glucuronidated conjugates of these derivatives.[180,196,197]

Tolerance to cannabinoids is mainly due to PD rather than PK mechanisms, because of changes in CB1 receptor availability.[137,198] Two mechanisms by which this occurs are receptor desensitization and receptor downregulation (internalization/degradation of receptor).[137,199] PK tolerance, while not as common as PD tolerance, is a possibility and is mainly due to changes in absorption, distribution, and excretion.[137,200] In humans, tolerance is seen after a few doses and disappears rapidly following cessation, with tolerance developing to mood, intra-ocular pressure, psychomotor performance, nausea, and cardiovascular system effects.[137,201,202]

Dosing is an obstacle for health-care professionals prescribing CBM, as the association between successful dose and disease state is still unknown. Therefore, dosing relies heavily on self-titration.[137] The approach for CBM dosing is to "start low, go slow, and stay low",[155] as most adverse effects of CBM, due to THC, occur early and are seen with high initial doses.[155] As patients develop tolerance to psychoactive effects of cannabis quickly over a period of days, without tolerance to the benefits, they can maintain the same dose for many years.[155]

1.6 Cannabis-Based Medicine

CBM is currently used and under investigation for the treatment of many different disorders including AIDS wasting syndrome, chemotherapy-associated nausea, Parkinson's disease, and epilepsy.[203] Cannabinoids may also be immunosuppressive and have therapeutic value in chronic inflammatory disorders, such as MS.[204]

1.6.1 Cannabis Products

Medicinal *Cannabis* products available include synthetic and naturally derived prescription products, as well as leafy *Cannabis*. Prescription products include nabiximols (oromucosal spray), cannabis extract (oral capsule), dronabinol (oral capsule), and nabilone (oral capsule).[205–208] In Canada, leafy *Cannabis* has been legal for medical use since 2001,[107] with prescription CBM products available since 2005.[209,210]

Two naturally derived *Cannabis* products are available, nabiximols (Sativex), and *Cannabis* extract (Cannador). Nabiximols, a 1:1 THC:CBD oromucosal spray derived from the *Cannabis sativa* plant,[211] is approved in 29 countries outside the US,[208,212] including the UK,

Spain, Poland, Germany, Denmark, the Czech Republic, Sweden, New Zealand, and Canada.[213] It has been approved in Canada since 2005 for the treatment of MS pain,[209] and was later approved for cancer-related pain (2007) MS spasticity (2010).[209,210,214,215] *Cannabis* extract (Cannador), is most commonly a 2:1 THC:CBD oral capsule.[208,216] It has be utilised in research studies across Europe and is produced by the Institute for Clinical Research (Berlin, Germany).[208,216] It has undergone testing in clinical trials for stiffness, spasms, and pain in multiple sclerosis, and for anorexia/cachexia in cancer subjects.[216] Cannador is not available in the United States[208] or Canada.[217]

Dronabinol (Marinol) and nabilone (Cesamet) are two synthetic oral cannabinoid products.[205,218] Dronabinol has been approved in the United States since 1985 and is used for the treatment of nausea/vomiting associated with chemotherapy, and anorexia due to AIDS weight loss.[208,219] Dronabinol was previously available in Canada, but was voluntarily withdrawn from the Canadian market by its manufacturer[205] for unspecified reasons.[220] Nabilone is approved in both Canada and the United States for chemotherapy-associated nausea and vomiting.[208,221,222]

In 2018, the FDA approved Epidiolex (cannabidiol) for the treatment of Lennox-Gastaut syndrome and Dravet syndrome in children two years and older.[223] This was the first marijuana-derived drug approved by the FDA.[223]

As both naturally derived (nabiximols, *Cannabis* extract) and synthetic (dronabinol, nabilone) prescription products are available, it is important to consider that these two types of products may behave differently to produce varied pharmacological effects. Synthetic cannabinoids have differences in selectivity, potency, and function compared to naturally derived cannabinoids. The synthetic cannabinoids demonstrate greater potency than those that are naturally-derived.[224]

1.7 Efficacy of Cannabinoids for MS in Animal Models

Current literature suggests that CBM has therapeutic benefit for MS symptom treatment. A main source of concern with CBM use is the possibility of adverse effects, particularly psychoactivity. Current human studies indicate that side-effects are generally well-tolerated,[225] with the most common ones being dizziness and dry-mouth.[226] Additionally, many unanswered

questions remain with respect to CBM, including formulation (which cannabinoid(s) to use), dose, and route of administration. Animal studies have evaluated the efficacy of various cannabinoids on mitigation of MS symptoms and disease progression.

1.7.1 Disease Progression

Studies using synthetic cannabinoids have investigated the efficacy of these compounds with respect to disease progression of animal models of MS. Dexanabinol, a synthetic cannabinoid, reduces inflammation in the brain and spinal cord of experimental autoimmune encephalomyelitis (EAE) animals, thus suppressing disease progression.[227] Likewise, mice infected with Theiler's murine encephalomyelitis virus (TMEV) were used to test the efficacy of three synthetic cannabinoids, WIN 55, 212-2, ACEA, and JWH-105, on the progression of the disease. These cannabinoids may hinder demyelination and inflammatory processes and favour myelin repair, therefore improving neurological deficits of the disease, and allowing for recovery.[228] Histological studies also determined reductions in microglial activation and a decreased number of infiltrating T-cells in the spinal cords of the TMEV mice that were treated with the cannabinoids.[228] Therefore, these studies suggest a therapeutic benefit to using cannabinoids in demyelinating diseases.

The use of phytocannabinoids, THC and CBD, on EAE disease progression in rats demonstrated that THC inhibited clinical and histological signs of EAE. Since there was significantly less inflammation in histological studies, THC may be effective at EAE suppression and prevention.[229] As well, CBD administration at the time of viral infection ameliorated motor deficits, which was associated with reduced microglial activation and pro-inflammatory cytokine production.[230] These studies emphasise the anti-inflammatory and immunomodulatory effects of both THC and CBD, and show therapeutic potential of CBM for the treatment of MS.

Additionally, evaluation of cannabinoid receptor involvement in MS animal models suggest the importance of the CB1 receptors in disease progression. CB1 receptor knockout mice demonstrated poor tolerance to inflammatory and excitotoxic insults, and subsequently went on to develop substantial neurodegeneration after chronic relapsing experimental autoimmune

encephalomyelitis (CREAE) induction.[231] In this model, CB1 agonists provide significant neuroprotection and slow the neurodegenerative process of MS in control mice.[231]

1.7.2 Spasticity

In addition to disease progression, animal models of MS are used to assess cannabinoids' efficacy at treating the symptoms of MS. The most commonly studied symptom is spasticity. Much evidence suggests CBM is a useful option. In a CREAE model of MS, the CB receptor agonists, R(+)-WIN 55,212, THC, methanandamide and JWH-133, improve both tremor and spasticity, while CB1 and CB2 receptor antagonists, SR141716A and SR144528, exacerbated tremor and spasticity.[222] Such data suggests the endogenous cannabinoids may be tonically active.[232] The presence of endocannabinoids in a CREAE mouse model of MS, in relation to their influence on spasticity, have also been evaluated. Enhanced levels of endocannabinoids, including anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), were demonstrated as compared with control or non-spastic CREAE mice.[232] Additionally, inhibitors of endocannabinoid re-uptake and hydrolysis had a positive impact on spasticity similar to the cannabinoid receptor angonists.[232] This again suggests a tonic control of spasticity by the endocannabinoids that could lead to therapies for MS symptoms.

In a comparative study of the effects of CBM and baclofen on spasticity in CREAE mice, THC:CBD (in a 1:1 ratio) demonstrated a dose dependent decrease in spasticity, with high doses showing similar reductions to baclofen.[233] In addition to exhibiting similar efficacy, CBM has no withdrawal period, a distinct advantage to baclofen where withdrawal from this drug needs to be done slowly to avoid dramatic side effects.[233] Furthermore, Pryce and Baker[234] tested the involvement of CB1 and CB2 receptors in spasticity and found that spasticity was induced in CB1 knock-out mice after EAE induction, and that CB1 receptor agonists control spasticity and CB2 receptor agonists have cross-reactivity, accounting for their therapeutic effect. Despite the fact that psychoactivity is due to CB1 receptor agonism,[234] the CB1 receptor might be the main target for spasticity related to MS, as it has the greatest therapeutic effect.[234]

1.7.3 Limitations of Animal Studies

Animal models are necessary for understanding the underlying mechanisms of MS and developing possible treatments. However, no animal model is able to fully capture all aspects (clinical, radiological, pathological and genetic) of MS due to its complex nature.[235] Therefore, supplementation of animal studies with human clinical trials is necessary to fully understand the range of effects of various pharmacotherapies in humans.

1.7.4 Side Effects and Toxicity

The most common side effects of CBM observed in human clinical trials include dizziness, dry mouth, and somnolence.[226] However, most human studies report few adverse events and usage is generally well tolerated,[225] especially if dose titration is used to help minimize adverse events.[236,237] THC has a wide safety margin, and it is difficult to determine a toxic dose given the variation in purities and exposure routes;[238] however THC is intoxicating.[239] CBD has a good safety profile, and is associated with few side effects or toxicity.[240] Long-term effects of CBM are still unknown as research in this area is limited. Thus far, no association between *Cannabis* use and death has been noted,[241,242] though smoking *Cannabis* can lead to various respiratory issues.[243,244]

1.8 Rationale

Potential of CBM to treat MS is seen in the increase of *Cannabis* use by individuals with MS, the preliminary research done in MS animal models, and the approval of CBM by Health Canada. A systematic review on the use of CBM in MS will help further evaluate its potential role as a therapeutic option in managing the disease and for identifying areas of potential research.

1.9 Research Question

How is cannabis-based medicine (CBM) used for the treatment of multiple sclerosis and its associated symptoms?

1.10 Purpose

This thesis will describe the use of CBM for the treatment of MS symptoms and disease progression and explain the forms of CBM used by the MS population.

1.11 Objective

Conduct a systematic review of the literature on the use of CBM to treat MS and its symptoms.

CHAPTER 2: METHODS

2.1 Search Strategy

A literature search was completed using MEDLINE (Ovid Medline® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline® Daily and Ovid Medline® 1946 to Present), *International Pharmaceutical Abstracts* (International Pharmaceutical Abstracts 1970 to February 2018), and Embase (Embase Classic + Embase 1947 to 2018 Week 41). A preliminary search was completed on August 29, 2017, and re-run on October 11, 2017 and February 26, 2018 to identify additional articles (Table 2.1). Systematic review articles and bibliographies of relevant articles were hand searched for inclusion of potential studies. Grey literature was not searched.

2.2 Inclusion and Exclusion Criteria

All articles published in English that were MS-specific and involved human subjects were eligible for inclusion. Both randomized controlled trials and observational studies were included; however, individual case reports were not. No publication year limit was applied.

2.3 Review Methods and Quality Assessment

All duplicate records were identified electronically by Mendeley and removed. In DistillerSR (Evidence Partner, v2) two reviewers (NB and NA) initially screened titles for eligibility, and then the full abstracts. Complete copies of the articles deemed potentially relevant were obtained and reviewed independently by both reviewers to determine if they should be included. Discrepancies were resolved by a third party (CE) not involved in the original review. Data were abstracted into a standardized form by both reviewers and included the following information: author, year, study location, study cohort size ("n"), study type/design, primary endpoint, study cohort characteristics (e.g. age, sex, MS type/severity), type of product used (CBD, THC, both), route of administration, dose, dose regime, comparator, study length, primary endpoint results, reported adverse effects, number of patients that withdrew from the study (with reasons, if reported), and notes of interest (e.g. possible author affiliations). If a primary outcome

was not specified, the outcome specified in a power calculation was considered the primary outcome. If there was no power calculation, then the first outcome reported in the results section was considered to be the primary outcome.[245]

Quality assessment was also performed independently by both reviewers (NB and NA) using a modified Downs and Black checklist (Appendix A).[246,247] The maximum score on the checklist is 28, with categories of good (20-28), fair (15-19), and poor (≤ 14).[247] Any scoring discrepancies were resolved by a third party (CE). Given the heterogeneity of the studies, a meta-analysis was not performed.

Table 2.1. MeSH terms and key words for each database

Database	**Search Terms (26/02/18)**	
Embase (Embase Classic + Embase 1947 to 2017 Week 41)	• THC • Cannabis sp • Marinol • Hashish • Hash Oil • Nabilone • Epidiolex • Cannabis • Cannabi* • Medical cannabis • Medical marijuana **Results: 1647**	• Marijuana • Marihuana • Sativex • Dronabinol • Dronabinol • Nabiximols • Nabiximols • Demyelinating disease • Multiple sclerosis (explode) • Disseminated sclerosis • Multiple sclerosis
Medline (Ovid Medline® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline ® Daily and Ovid Medline ® 1946 to Present)	• THC • Cannabis sp • Nabilone • Epidiolex • Medical marijuana • Cannabis • Cannabi* • Marijuana • Marihuana **Results: 741**	• Medical marijuana • Sativex • Nabiximols • Dronabinol • Dronabinol • Demyelinating disease • Multiple sclerosis (explode) • Multiple sclerosis • Disseminated sclerosis
International Pharmaceutical Abstracts (IPA) (International Pharmaceutical Abstracts 1970 to September 2017)	• Medical marijuana • Cannabi* • Sativex • Marijuana • Marihuana • Dronabinol • Nabiximols **Results: 68**	• THC • Cannabis sp • Nabilone • Epidiolex • Multiple sclerosis • Disseminated sclerosis • Demyelinating disease

CHAPTER 3: RESULTS

3.1 Study Selection

Initially, 2756 articles were identified, of which 468 were deemed potentially eligible, after title and abstract screening. A total of 60 articles were included in the final review (Figure 3.1). Of these 60 articles, 26 were randomized control trials (RCTs) and 34 were observational studies. Of the 26 RCTs, 15 used intention to treat (ITT) analysis.

Studies were published between 1981 and 2018, with the majority published after 2010 (Tables 3.2-3.16). The articles were categorized according to the primary outcome: spasticity (n=29), pain (n=8), cognitive function (n=6), adverse events/safety (n=6), bladder dysfunction (n=4), balance/walking (n=3), tremor (n=1), progression (n=1), and general symptoms (n=2). Results were then further categorised by assessment method to allow for comparability. Study lengths ranged from one day to over three years. Most included studies were less than six months in length.

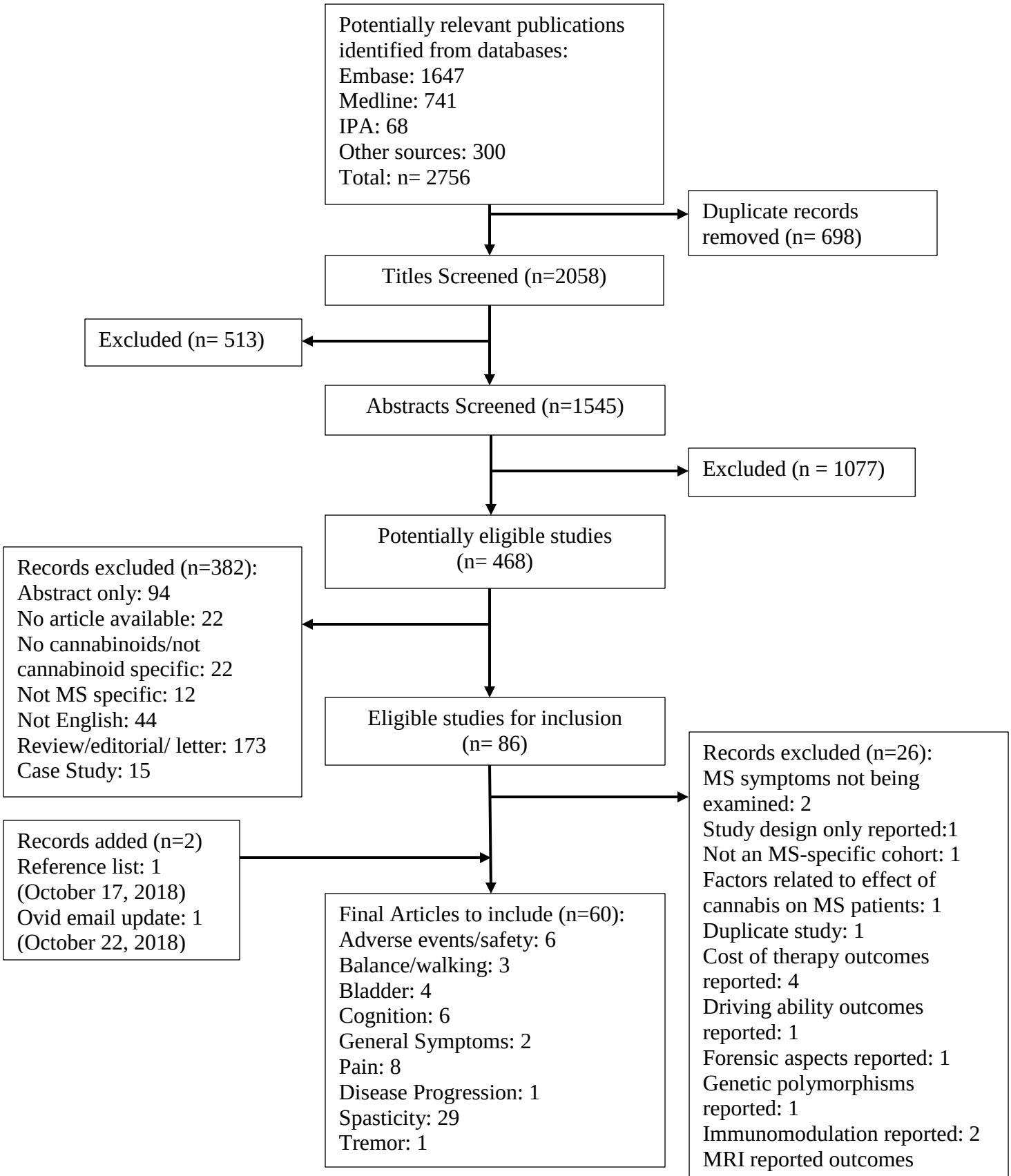

Figure 3.1. Flow diagram of article inclusion[248]

Most studies evaluated the use of the oromucosal spray nabiximols (Sativex®) (2.7 mg THC, 2.5 mg CBD/100 µL spray), a pharmaceutical grade product. Several studies involved other CBM formulations and dried *Cannabis*. The route of administration, dosing schedules, and ratio of Δ^9-THC:CBD all varied among studies.

Table 3.1. *Cannabis*-based medicine interventions

Generic Name (Trade Name)	Route of Administration	Manufacturer	Dosage
Cannabis Extract (Cannador)	Oral	Institute for Clinical Research, Germany	Ratio of 2.5 mg THC:1.25 mg CBD, <5% other cannabinoids[56,249,250] Ratio of 0.8-1.8 mg CBD:2.5 mg THC[70]
Cannabis Extract (Cannador)	Oral	Society for Oncological and Immunological Research, Germany	Ratio of 2.5 mg THC, 20 to 30% CBD and <5% other cannabinoids[251] Ratio of 2.5 mg THC:0.9 mg CBD[225] Ratio of 2.5 mg THC:1.25 mg CBD, <5% other cannabinoids[62]
Nabiximols (Sativex)	Oromucosal	GW Pharmaceuticals	Ratio of 2.7 mg THC:2.5 mg CBD[45,46,226,236,237,252–258,48,259–268,51,269–278,54,55,57,58,77,82]
Dronabinol (Marinol)	Oral	Solvay Pharmaceuticals	3.5 mg THC[279] 2.5 mg THC[50,56,67,249–251,280]
Nabilone (Cesamet)	Oral	Not Stated	THC 0.5 or 1 mg capsules[281]
ECP002A	Oral	Echo Pharmaceuticals B.V.	1.5 mg or 5 mg THC[282]
Smoked	Inhalation	National Institute on Drug Abuse (USA)	4% THC[283]
Smoked	Inhalation	Not Stated	1.54% THC[284]
Smoked (Street *Cannabis*)	Inhalation	N/A	Varies[81,285–287]
Synthetic THC	Oral	Not Stated	10 mg or 15 mg THC[49]

CBD: cannabidiol; N/A: not applicable; THC: Δ^9-tetrahydrocannbinol; USA: United States of America

According to the modified Downs and Black assessment tool, 23/60 (38%) articles were considered poor quality, 14/60 (23%) fair quality, and 23/60 (38%) good quality. All the articles that were rated as good were published 2003 or later. Thirty-two studies clearly identified a primary outcome measure in the introduction or methods, and 15 studies were adequately powered for their primary endpoint. Common methodological issues included non-randomized designed, inadequate blinding, no power calculation, and lack of consideration for confounding factors or subjects lost to follow-up.

3.2 Spasticity

Spasticity was assessed in 29 articles (Tables 3.2-3.5). Eleven were RCTs and eighteen were observational studies. Ten studies were good quality, nine were fair quality, and ten were poor quality. Twenty-two of these studies used nabiximols (Sativex), three used oral *Cannabis* extract (Cannador) with varying ratios (2:1 THC:CBD and 3:1 THC:CBD), five used oral THC (dronabinol and ECP002A), and one used inhaled CBM. The assessment measures used included both objective and subjective spasticity measures. Six good quality studies found CBM statistically beneficial for the treatment of spasticity.

3.2.1 Studies Assessed with the Ashworth Scale or Modified Ashworth Scale

Seven studies,[225,249,250,269,270,273,283] four RCTs and three observational studies, assessed MS-related spasticity with either the Ashworth scale or modified Ashworth scale (MAS) (Table 3.2). Two of these studies were good quality, and significantly favoured CBMs; a 3-day RCT with crossover design utilizing a *Cannabis* cigarettes (4% THC),[283] and a 12-month follow-up study using oral *Cannabis* extract (2:1 THC:CBD) and dronabinol (2.5 mg THC).[249] Two good quality studies found no statistical benefit from using dronabinol[250] or *Cannabis* extract.[225,250] Adverse events (dizziness, nausea, fatigue) were generally well tolerated and were similar for all products used.

Table 3.2. Spasticity assessment with Ashworth or modified Ashworth scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Zajicek et al. 2003[250]	RCT	13 weeks	18–64 years; stable disease for the previous 6 months; Ashworth score of 2 in two or more lower limb muscle groups; treatment not altered in the 30 days before the start of treatment. No ischaemic heart disease, infections, fixed-tendon contractures, severe cognitive impairment, history of psychotic or major illness, pregnancy, use of THC at any time, and use of cannabis in the 30 days before the start of the study, foreign travel immunisations over the 15 weeks of the study, taking medication such as beta interferon.	Change in Ashworth scale from baseline to the end of the 13-week treatment period	Dronabinol (Marinol) (n=216) Oral *Cannabis* extract (n=219) Maximum dose of 25 mg daily, depending on body weight	Placebo (n=222)	No evidence of effect of treatment. Mean changes in total Ashworth scores (baseline to 13 weeks' follow-up) were 1.24 (*Cannabis* extract), 1.86 (THC), and 0.92 (placebo) p=0.29	Dizziness or light-headedness, dry mouth, constipation, diarrhoea, increased appetite. One MS relapse in each treatment group and 7 in the placebo group. More adverse events with THC-only treatment.	Good (23)
Vaney et al. 2004[225]	Randomised, double-blind, placebo-controlled cross-over study	14 days	Clinically stable spasticity with at least one joint scoring >/= 2 on the Ashworth scale. No significant neurological (other than MS), cardiovascular, or infectious diseases; clinical disease exacerbation or treatment with steroids during the two months preceding study entry; history of alcohol or drug abuse; depression, history of psychosis; use of cannabinoids during the	Change in the Ashworth scale of muscle tone after 14 days of active treatment	Oral *Cannabis* extract (Cannador) (n= 57) Maximum dose of 30 mg THC/day	Placebo	Placebo period: 13.1 +/- 6.3 (baseline) to 11.5 +/- 6.1 (14 days) Cannabis period: 12.2+/- 6.4 to 11.6 +/- 6.5 Difference: -0.8+/-1.3 p=0.2379	No serious adverse events reported. Most common were dizziness, euphoria (high), difficulty concentrating (in both active and placebo groups)	Good (24)

Table 3.2. Spasticity assessment with Ashworth or modified Ashworth scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			week prior to inclusion; or significant cognitive impairment (Short Orientation Memory Concentration Test < 21).						
Corey-Bloom et al. 2012[283]	Randomised, double-blind, placebo-controlled crossover trial	3 days	Spasticity with at least moderate increase in tone (score ≥ 3 points on the modified Ashworth scale at the elbow, hip or knee); subjects were allowed to continue other treatments for spasticity, with the exception of benzodiazepines, if they had been taking stable doses for three months or longer; subjects could continue disease -modifying therapy if they had been on a stable regimen for at least six months; no medication changes that would affect spasticity scores. No patients with a history of major psychiatric disorder (other than depression) or substance abuse, substantial neurologic disease other than MS and severe/unstable medical illnesses, known pulmonary disorders, patients who used benzodiazepines to control spasticity or high doses of	Change in spasticity as measured by patient score on the modified Ashworth scale before treatment to end of three days of treatment	Smoked *Cannabis* cigarette (n=30) 4% THC by weight, 800mg cigarette Average of 4 puffs/cigarette	Placebo	Smoking cannabis improved patient scores on the modified Ashworth scale by an average of 2.74 points more than placebo p=0.001	Dizziness, headache, fatigue, nausea, feeling "too high", throat irritation	Good (22)

Table 3.2. Spasticity assessment with Ashworth or modified Ashworth scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			narcotic medications for pain, and those pregnant or breastfeeding. No *Cannabis* month before screening and during the trial.						
Tomassini et al. 2014[273]	Randomised double blind, placebo-controlled, crossover trial	3 weeks	Right-handed secondary-progressive MS patients with normal right hand function, EDSS score between 3.5 and 6.5; clinically stable disease for the preceding 30 days; spasticity in at least two muscle groups (score ≥ 2 on the Ashworth scale for each muscle group); stable antispastic treatment in the preceding 4 weeks; no disease modifying therapies started in the preceding 6 months; no clinical condition precluding safe participation; no cannabinoid use or concomitant therapy with antidepressants, psychoactive drugs, corticosteroids prior to the study entry.	Change in total Ashworth score between baseline and 3-weeks of cannabinoid use	Nabiximols (Sativex) (n=18) Maximum dose of 48 sprays/day Median sprays/day: 7.4	Placebo	Mean change (post vs. pre) in total Ashworth scale was -0.664 for Sativex and -0.83 for placebo p=0.48	Well tolerated with minor adverse events such as fatigue, nausea and dizziness.	Poor (11)
Zajicek et al. 2005[249]	Follow-up study	12 months	18–64 years, stable disease for the previous 6 months (in the opinion of the treating physician, rather than as measured by EDSS) and problematic spasticity (Ashworth score of at least	Mean change in Ashworth score from baseline (start of main study) to the end of the	Dronabinol (Marinol) (n=216) Oral *Cannabis* extract (n=219) maximum of 25 mg THC daily,	Placebo (n=222)	Mean improvements from baseline to 12 months: THC 1.82, cannabis extract	No major safety concerns. Minor adverse events were reported by 361 patients	Good (23)

Table 3.2. Spasticity assessment with Ashworth or modified Ashworth scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			2 in two or more muscle groups).	follow-up period	depending on body weight		0.10, placebo -0.23 p=0.04	(109 on THC, 125 on cannabis extract, 127 on placebo), and included: relapse/possible relapse, UTI, pneumonia/chest infection, seizure, insertion of baclofen pump, limb fracture	
Russo et al. 2015[269]	Observational	30 days	Age > 18 years, diagnosis of MS since at least six months, moderate to severe spasticity in at least two districts of upper and/or lower limbs, absence of clinical or neuroradiological relapses at least six months prior to study entry, EDSS score >3.5, no history of psychosis, no presence of pace-maker, aneurysms clips, or neurostimulator or brain/subdural electrodes. All subjects were taking antispastics, with baclofen being the most common.	Assessment of spasticity using the MAS after 30 days of treatment	Nabiximols (Sativex) (n=37)	N/A	MAS: T_0: 4+/-0.7 T_{30}: 3+/-0.9 p=0.01	After 1 month of nabiximols, the main adverse events in the whole sample were dizziness, dry mouth, nausea, and weakness.	Poor (12)
Russo et al. 2016[270]	Observational	1 month	MS for at least 6 months, 18 years of age, no clinical or neuroradiological relapses for at least 6 months prior to	Change in MAS score in pain and no-pain MS patients before	Nabiximols (Sativex) (n=20; 10 with neuropathic pain, 10 without)	N/A	Mean MAS Score:	The most commonly reported adverse events	Poor (14)

Table 3.2. Spasticity assessment with Ashworth or modified Ashworth scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			study entry, an EDSS score 3.5, right-handedness, right side being the most affected, no history of psychosis, no safety contraindication for TMS/laser procedures. Patients with severe pain from other concomitant conditions were excluded.	and after treatment	Mean 8-9 sprays/day		No pain group before treatment: 4 No pain group after treatment: 2 Pain group before treatment: 4 Pain group after treatment: 2 Pain group: p=0.03 No pain group: p=0.03	were dizziness, dry mouth, nausea, and weakness. No significant changes were observed in BP, weight, temperature, and blood tests	

BP: blood pressure; EDSS: expanded disability status scale; MAS: modified Ashworth scale; MS: multiple sclerosis; N/A: not applicable; RCT: randomized controlled trial; THC: Δ^9-tetrahydrocannabinol; TMS: transcranial magnetic stimulation; UTI: urinary tract infection

3.2.2 Studies Assessed with the Numerical Rating Scale

Thirteen studies assessed MS-spasticity using the numerical rating scale (NRS) (Table 3.3).[254,255,268,274,277,257–259,261,263–266] All thirteen studies utilized nabiximols (Sativex). Three studies were RCTs and ten were observational. Three good quality studies found a statistically beneficial effect with nabiximols (Sativex) use.[254,258,263] One good quality study found no statistical benefit with use of nabiximols (Sativex).[255] Adverse events (AEs) were generally well tolerated with dizziness and fatigue being commonly reported; however, some studies also reported cognitive/psychiatric disturbances.[259,265,266]

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Collin et al. 2007[254b]	RCT	6 weeks	>18 years of age, stable disease for at least 3 months before study entry; significant spasticity in at least two muscle groups (Ashworth score ≥ 2 or more; not getting adequate relief using current therapy; stable treatment for at least 30 days before entry and during the study. Effective contraception for subjects of childbearing potential. Use of cannabis or cannabinoids prohibited during the study and for at least 7 days before visit 1. No psychosis or severe psychiatric disorder other than depression, known alcohol or substance abuse, severe cardiovascular disorder, history of seizures, pregnancy/lactation, planned travel abroad during the study.	The change from baseline in the severity of spasticity based on a daily diary assessment by the subject on NRS to the end of the treatment period (6 weeks)	Nabiximols (Sativex) (n= 124) Maximum dose of 48 sprays/day Mean dose of 9.4 sprays/day	Placebo (n= 65) Mean dose of 14.7 sprays/day	Mean change in NRS spasticity scores for the CBM group at the end of treatment improved by 1.18. The placebo group improved by 0.63 points. The estimated treatment difference was 0.52 points, in favour of the Sativex group p=0.048	Dizziness, fatigue, UTI, dry mouth	Good (20)
Collin et al. 2010[255b]	RCT	99 days	MS of at least 6-months duration, and at least a 3-month history of spasticity due to MS (not wholly relieved with current therapy). Anti-spasticity regimen stable for at least 30	Mean change in NRS spasticity score from baseline to the last 14 days of treatment period.	Nabiximols (Sativex) (n= 167) Maximum dose of 8 sprays/3hrs, and 24 sprays/day	Placebo (n= 170) Mean dose of 15.4 sprays/day	Mean change in treatment NRS score from baseline to 14 days' treatment was an improvement of 1.05 points.	Most common AEs higher in the Sativex group; dizziness, fatigue, somnolence,	Good (20)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			days preceding study entry. No subjects with symptoms of spasticity not due to MS, concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders.		Mean dose of 8.5 sprays/day		Mean change in placebo NRS score from baseline to 14 days' treatment was an improvement of 0.82 points. Treatment difference: -0.23 points, in favor of the Sativex group. p=0.219	nausea, asthenia, vertigo	
Novotna et al. 2011[263b]	RCT	16 weeks	MS for at least 6 months; spasticity because of MS for at least 3 months (not wholly relieved with current medication), at least 20% reduction in NRS score in phase A; No new alterations of medications from Phase A. No concomitant disease or disorder that had spasticity-like symptoms; medical history that suggested that relapse/remission was likely to recur during the study, no cannabis or cannabinoid use 30-days prior to study entry, concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders,	Change in spasticity NRS from the point of randomization to the end of 12 weeks of treatment	Nabiximols (Sativex) (n=124) Maximum dose of 12 sprays/day Mean dose of 8.3 sprays/day	Placebo (n=117) Mean dose of 8.9 sprays/day	The mean spasticity score had further improved in the active treatment group by 0.04 units, from a baseline score of 3.87 points. In the placebo group, there was a mean deterioration of 0.81 from a baseline score of 3.92 points. The estimated treatment difference between the two groups in mean spasticity NRS was 0.84 points (95% CI: 1.29 to 0.40). This difference was	Overall AEs similar between nabiximols and placebo; no event occurred at a rate greater than 10% in either group; most common AEs in nabiximols group were: vertigo, fatigue, muscle spasms, UTI, dry mouth	Good (21)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			known or suspected history substance abuse.				highly statistically significant (p = 0.0002).		
Flachenecker et al. 2014[259b]	Observational	12 months	≥18 years of age, moderate to severe MS spasticity (spasticity causing limitations activities of daily living, activities in social environment, or where there is a risk of spasticity-related complications), start of nabiximols at inclusion, patients characteristics according to labelling or nabiximols, consent, completion of initial MOVE 2 study. No spasticity not due to MS, cognitive impairment, deficits of German language.	Degree of spasticity, as measured by the NRS, after 12 months of treatment with nabiximols	Nabiximols (Sativex) (n=104) After 12 months, the mean number of sprays was 6.2 +/- 2.6 (range of 2-12)	N/A	Mean NRS score showed a significant improvement from 6.2 at BL to 4.6 at 12 months follow-up. p=0.0001	22 AEs recorded in total: GI Disorders, Psychiatric Disorders, Nervous System Disorders, Skin and Subcutaneous Tissue Disorders, General Injury, Poisoning and Procedural, Eye Disorders. All reported AEs were considered casually related to nabiximols	Fair (17)
Flachenecker et al. 2014[258b]	Observational	3-4months	>18 years of age, moderate to severe MSS, start of nabiximols at inclusion (start of nabiximols no more than 7 days before inclusion and prescription decision independent of study participation), patient characteristics according to labeling of	Effectiveness of nabiximols through degree of spasticity, as measured by the NRS, after one month of treatment	Nabiximols (Sativex) (n=300) Mean dose of 6.9 sprays/day	N/A	At baseline, mean spasticity NRS score was 6.1 points in the entire study population, and after one month this value improved by 12.3% to 5.2 points p=0.0001	8 serious AEs: despondency, fatigue, weakness, worsened walking ability, dizziness, headache, muscle spasms, UTI.	Good (20)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			nabiximols, and signed consent. No spasticity due to causes other than MS, patients with relevant cognitive impairment, deficits of German.						
Koehler et al. 2014[261b]	Observational	9 months	All patients with MS spasticity who began treatment with THC:CBD spray between September 2011 and January 2013 at the Marianne Strauss hospital in Berg, Germany	Change in NRS score in the first 10 days of treatment	Nabiximols (Sativex) (n=166) Mean dose of 4 sprays/day	N/A	Mean NRS score in responders was 7.0 before treatment and decreased to 3.0 within the first 10 days of treatment, representing a 57% improvement.	Most common AEs leading to discontinuation: dizziness, fatigue and oral discomfort	Poor (12)
Torjano and Vila 2015[274b]	Observational	3 months	≥ 18 years of age; moderate-to-severe spasticity; start Sativex at time of enrollment; patient signed consent; concomitant medication and other management approaches are stable unless change is indicated in patients' clinical evaluation. No non-MS spasticity, relevant cognitive impairment, or deficits of relevant language.	Improvement in NRS scores from baseline after 3 months	Nabiximols (Sativex) (n=322) Mean dose of 6.1 sprays/day at visit 1, and 5.1 sprays/day at visit 3	N/A	At BL, mean NRS score was 6.8 points (n=242). The score decreased to 5.5 points in patients with available data at 3 months (n=166), showing a significant 19.1% improvement p=0.0001	Dizziness, confusion, somnolence, nausea	Fair (16)
Ferre et al. 2016[257c]	Observational	48 weeks	Moderate-to-severe spasticity due to MS (NRS score of ≥4); have evidence of no adequate	Change in NRS score at 4-week follow-up	Nabiximols (Sativex) (n=144)	N/A	Mean NRS score was stable in non-responders (7.2	116 out of 144 patients (80.5%) reported adverse events	Fair (19)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			response to traditional antispastic medications. No subjects use of cannabis or cannabinoids in the 30-days prior treatment start, known history of psychiatric disorders, cardiovascular diseases or epilepsy.		Mean dose of 6.5/day for responders and 7.7/day for non-responders		at baseline and 7.5 at 4 weeks, (p = 0.275), whereas it significantly improved in responders from 7.6 at baseline to 5.2 at 4 weeks p=0.001	Most common AEs: confusion/ideo motor slowing, dizziness and fatigue.	
Paolicelli et al. 2016[264c]	Observational	Mean follow-up period was 40 +/- 28 weeks	MS patients treated with Sativex and followed at the MS Center of the University of Bari.	Change in the NRS spasticity score from baseline to first month follow-up.	Nabiximols (Sativex) (n=102) Mean dose of 6.5 sprays/day	N/A	Mean improvement in NRS score of 2.5 points, from the value of 8.7 at the baseline assessment to a value of 6.2 at the first month follow-up. p= 0.0001	A total of 41 subjects had AEs: dizziness, nausea, asthenia, bewilderment, drowsiness, oral hyperalgesia, anxiety, decline in attention/concentration, diarrhea, alterations of dental enamel, lack of appetite, seizures.	Poor (13)
Patti 2016[266c]	Observational	6 months	Resistant to other medications for MS spasticity with a score of ≥ 4 on the spasticity 0–10 NRS No severe cardiovascular disease or psychiatric disorders, pregnant women, individuals known to use psychoactive	Change in NRS scores at 1-month follow-up	Nabiximols (Sativex) (n=1534) Mean dose of 6.8 sprays/day	N/A	61.9% of the population had ≥ 20% NRS improvement and remained on treatment. 25% of the cohort had achieved clinically relevant ≥ 30% NRS	Cognitive/psychiatric symptoms, fatigue, drowsiness, dizziness, GI symptoms, oral discomfort	Fair (15)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			substances (e.g. street cannabis).				improvement at 1 month		
Patti et al. 2016[265c]	Observational	6 months	>18 years; NRS score ≥4; not responding to common and ongoing antispastic drugs (used under their approved label) No severe cardiovascular diseases, history of psychiatric diseases, use of street cannabis and/or other psychoactive drugs; MS spasticity NRS score <4	Change in MS NRS spasticity score (baseline vs 4 weeks of treatment)	Nabiximols (Sativex) (n=1615) The mean number of puffs per day was 6.8±2.6	N/A	Statistically significant improvement between BL and 4 weeks NRS score. At BL, the NRS score was 7.5, and at 4 weeks, the NRS score was 5.9 p=0.0001	55 cognitive/ psychiatric disturbances, 9 were cognitive, and 46 were psychiatric. Fatigue (n=36), drowsiness (n=32), dizziness (n=30), gastrointestinal symptoms (n=21), mouth discomfort (n=10), allergic reaction (n=3) and other neurological symptoms (n=16) were AEs considered drug related.	Fair (16)
Russo et al. 2016[268]	Observational	6 months	NRS ≥4; evidence of inadequate response to the traditional anti-spastic medications (thus, all the patients had to be in treatment with Sativex); age > 18 years; a diagnosis of definite MS since at least six months; right-handed with normal right-hand function; the absence of clinical or	Change in NRS score before and after 1 month of treatment	Nabiximols (Sativex) (n=61) Mean dose of 8-9 sprays/day	N/A	NRS at BL: 8 NRS at 1 month: 5 p<0.001	Main reported adverse events: dizziness, dry mouth, nausea, mild generalized weakness	Fair (17)

Table 3.3. Spasticity assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			neuroradiological relapses since at least six months; EDSS ranging from 3.5 to 8; no changes in anti-spastic and immune-modulator agents before their study enrollment; no history of psychiatric disorders, cardiovascular diseases or epilepsy; no use of cannabis or cannabinoid-based medications						
Vermersch et al. 2016[277b]	Observational	3 months	≥18 years of age, moderate-to-severe MS spasticity, THC:CBD prescribed up to 7 days before enrollment and independent of study participation, consent, must be national language, other medications stable for study. No spasticity due to reason other than MS, cognitive impairment.	Change in MS spasticity (measured by NRS scale) after 3 months treatment	Nabiximols (Sativex) (n=433) Mean dose of 6 sprays/day	N/A	Mean NRS score: 6.9 (BL) 5.4 (3 months) p=0.0001	No severe AEs; most common AEs: dizziness, confusion, asthenia, somnolence	Fair (16)

AE: adverse event; BL: baseline; CBD: cannabidiol; EDSS: expanded disability status scale; GI: gastrointestinal; MS: multiple sclerosis; MSS: multiple sclerosis spasticity; N/A: not applicable; NRS: numeric rating scale; RCT: randomized controlled trial; THC: Δ^9-tetrahydrocannabinol; UTI: urinary tract infection

[b]: study sponsored by pharmaceutical company

[c]: author affiliation with pharmaceutical company

3.2.3 Studies Assessed with the H/M Ratio

Three studies,[262,272,282] two RCTs and one observational study, used the ratio between the maximum H reflex and maximum M response (H/M ratio),[44] as an assessment measure (Table 3.4). One good quality[282] and two fair quality studies[262,272] found no significant treatment effect with 4 weeks of nabiximols (Sativex) or oral THC use. All three studies were published since 2015. Common adverse events included dizziness and somnolence, and were mild and well tolerated.

Table 3.4. Spasticity assessment with H/M ratio

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Leocani et al. 2015[262b]	Randomised, double-blind, placebo-controlled, crossover study	4 weeks	≥18 years of age; progressive primary or secondary MS of at least 12 months' duration; relapse-free for at least 3 months prior to screening; EDSS score between 3.0 and 6.5; MAS score of at least ''1+'' in one limb; stable antispasticity medication 2 months prior to screening. No modifications to DMTs 6 months prior to or during the study. No concomitant disease that will cause/interfere with spasticity; botulinum toxin injection for spasticity in the 4 months prior to screening; any known or suspected history of psychotic illness, alcohol or substance abuse; epilepsy or hypersensitivity to cannabinoids; significant cardiac, renal or hepatic disease; pregnant or lactating, or subjects of child-bearing potential unless willing to use contraception; known contraindications to Sativex	The treatment effect on the H/M ratio from baseline to 4 weeks	Nabiximols (Sativex) (n=22) Maximum dose of 12 sprays/day Mean dose of 7 sprays/day	Placebo (n=22) Mean dose of 10 sprays/day	Mean H/M Ratio Sativex: BL: 0.33, week 4: 0.31 Placebo: BL:0.31; week 4: 0.31 No significant difference in the change from baseline to week 4 in the H/M ratio under treatment with Sativex or placebo p=0.40	Adverse events reported in 34 patients were: dizziness lower limb weakness vertigo, hypotension, hypertension, somnolence, pharyngodynia, and fever. One patient reported adverse events during both cycles (dizziness on Sativex and lower limb weakness on placebo), 13 patients to active treatment only, 5 patients to placebo only and 15 patients did not report any adverse events.	Fair (19)

Table 3.4. Spasticity assessment with H/M ratio

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
van Amerongen et al. 2018[282b]	RCT	4 weeks	≥18 years of age, diagnosis of progressive (primary or secondary) MS (revised McDonald criteria), disease duration of 41 years, clinically stable for at least 30 days before the start of the challenge phase. Ashworth score of ≥2 (range, 0-4) and a Kurtzke EDSS score between 4.5 and 7.5 at baseline (range, 0-10). Dosage and treatment regimen of spasmolytic therapy stable for at least 30 days before study participation and remained stable throughout study. Current use of Δ9-THC was exclusionary, as confirmed per urine drug screen.	Difference in the mean H/M ratio (change from baseline to 4-weeks of treatment) between placebo and ECP002A	ECP002A (tablets containing either 1.5mg or 5mg THC) Dose levels were 3, 5, and 8 mg (twice daily), leading to a total daily dose of 16mg. (n=12)	Placebo (n=12)	H/M ratio change from BL in placebo group was -0.002 and in active group was -0.008; there was no significant difference between the two groups p=0.8238	200 adverse events were recorded, most mild. The most commonly reported adverse events were dizziness and euphoric mood, followed by headache, somnolence, and fatigue.	Good (22)
Squntani et al 2016[272]	Observational	4 weeks	≥18 years of age, diagnosis of primary or secondary progressive MS least two years of disease or diagnosis of relapsing-remitting MS with a disease duration of at least 6 months, no clinical or radiological evidence of a relapse in the previous 6 months; presence of moderate to severe spastic hypertonia; failure of clinical response to other anti-spasticity medications. No contraindications to treatment with Sativex or to TMS execution.	Differences within the study population at baseline and 4 weeks as to both H-reflex and H/M ratio	Nabiximols (Sativex) (n=21) mean dose of 6.9 sprays/day	Healthy controls (n=19)	No differences within the studied population at BL and 4 weeks as to both H-reflex and H/M ratio. No differences were found when comparison of baseline or follow-up scores was made between patients and HCs	Only 3 patients complained of AEs (mild dizziness, and bitter taste)	Fair (15)

Table 3.4. Spasticity assessment with H/M ratio									
Reference	**Study Design**	**Intervention Length**	**Cohort Characteristics**	**Primary Outcome**	**Intervention (n=)**	**Comparator (n=)**	**Results**	**Adverse Events**	**Quality Score (/28)**
			Medications kept stable during the study.						

AE: adverse event; BL: baseline; DMT: disease modifying therapy; EDSS: expanded disability status scale; HC: healthy control; H/M ratio: H-reflex and M-response ratio; MAS: modified Ashworth scale; MS: multiple sclerosis; RCT: randomized controlled trial; THC: Δ^9-tetrahydrocannabinol; TMS: transcranial magnetic stimulation

[b]: study sponsored by pharmaceutical company

3.2.4 Studies Assessed with other outcome measures

Six studies,[45,46,48–51] used assessment measures not previously described (Table 3.5). Two studies were RCTs. Of these six measures, only one, the stretch reflex, is validated.[47] One study,[45] evaluating time to treatment failure, was determined to be of good quality, and reported significant improvement with nabiximols (Sativex). Adverse effects were generally mild and well-tolerated, with dizziness as a common adverse effect; one study did not report any adverse effects.

Table 3.5. Spasticity assessment (other outcome measures)

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Ungerleider et al. 1987[50]	Randomised, double-blind, placebo-controlled, crossover trial	5 days	Clinically definite MS and spasticity due to MS 26-64 years old, history intolerable adverse events from the use of other drugs	Patients' spasticity ratings BL vs end of treatment	Oral THC (n=13) escalating dose of THC between 2.5-15 mg; 7.5mg deemed optimum dose	Placebo	The level of spasticity reported by patients was lower in THC than placebo. Placebo: 3.4; THC: 2.23 p=0.03	Reported AEs: weakness, dry mouth, dizziness, relaxation, mental clouding, short-term memory impairment, spatial-time distortions. At 7.5 mg, there were no reports of intolerable adverse events.	Poor (13)
Notcutt et al. 2012[45b]	RCT	5 weeks	MS subjects receiving Sativex for spasticity at least 12 weeks prior to screening, and who were judged to have been receiving benefit from and showing tolerability to Sativex. Other spasticity medications were stable for at least 3 months prior to study entry and during the study. No concomitant disease or disorder that caused or influenced spasticity. No subjects unable to rate their level of spasticity or distinguish it from other MS symptoms. No subjects that received botulinum toxin or rimonabant 3 months prior to study entry. No history of	The time to treatment failure	Nabiximols (Sativex) (n=18) Mean dose of 7.7 sprays/day	Placebo (n=18) Mean dose of 9.0 sprays/day	Median TTF with Sativex: >28 days Median TTF on placebo: 1.50 days p=0.013	Pain (n=7, 2 receiving Sativex; 5 receiving placebo), muscle spasticity (n=5, 2 receiving Sativex; 3 receiving placebo), muscle spasms (n=4, 2 in each of the Sativex; and placebo groups) and depressed mood (n=2 subjects on placebo)	Good (23)

Table 3.5. Spasticity assessment (other outcome measures)

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders, no subjects with known or suspected history of substance abuse.						
Petro & Ellenberger 1981[49]	Placebo-controlled pilot study	Not specified	Spasticity, presumably of spinal origin and related to MS	Change in spasticity score after treatment	Oral synthetic THC (n=9) 10 mg or 15 mg *did not specify number of patients in treatment group vs placebo group	Placebo	The changes in spasticity scores between the groups at 180 minutes are significant ($p < 0.01$); summed scores for the two treated groups differed significantly from summed scores of the placebo group ($p<0.005$).	Minimal adverse effects: one patient reported being "high" after 10 mg, and another after placebo	Poor (5)
Fernandez et al. 2014[51]	Observational	Median exposure 174 days (23-1422)	Patients diagnosed with MS and treated with THC/CBD from the first time the treatment was used in April 2008 up to March 2014	Symptomatic treatment for refractory spasticity in MS patients during the study period (yes or no answer based on prescribing doctor's impression of a subject's response to treatment)	Nabiximols (Sativex) (n=56) Mean optimum maintenance dose of 5 sprays/day	N/A	Treatment was deemed highly effective in 80% of patients by prescribing physicians	Adverse effects were presented in 52% of subjects: dizziness (n = 11), muscle weakness (n = 7), somnolence (n = 6), diarrhea (n = 3), oral discomfort (n = 2), dry mouth (n = 2), blurred vision (n = 2), agitation (n = 1), nausea (n = 1), and paranoid ideation (n = 1).	Poor (13)

Table 3.5. Spasticity assessment (other outcome measures)

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Marinelli et al. 2016[46b]	Observational	4 weeks	Spasticity with MAS < 4 in at least one of the following: flexor muscles of the wrist, flexor muscles of the forearm, extensor muscles of the leg, foot plantiflexors,; no significant peripheral nervous system, no parkinsonism, no exposure to oral or smoked cannabinoids in the 30 days before starting study, no botulinum toxin injections and no dosage variation of other drugs that affects spasticity and pain 30 days before study, and nabiximols approved label requirements. No limitations related to age and degree of disability were applied for patient selection	Reduction of spasticity assessed with the stretch reflex after 4 weeks of treatment	Nabiximols (Sativex) (n=57) Maximum dose of 12 sprays/day Average dose of 6/7 sprays/day	N/A	The mean EMG improvement at 4 weeks in the 36 patients was statistically significant P=0.026	Main AEs: dizziness, sleepiness, nausea	Poor (11)
Messina et al. 2017[48c]	Observational	2 years (730 days)	≥18 years of age, NRS score ≥4, not responding to common and ongoing antispastic drugs (used under their approved label). No severe cardiovascular diseases, past history of psychiatric diseases, use of street	Discontinuation of Sativex during the observation period	Nabiximols (Sativex) (n=1596) Mean dose of 6.3 sprays/day	N/A	631 (39.5%) subjects discontinued therapy during the observation period	Not reported	Poor (12)

Table 3.5. Spasticity assessment (other outcome measures)

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			cannabis and/or other psychoactive drugs, pregnancy and MS spasticity NRS score <4.						

AE: adverse event; BL: baseline; CBD: cannabidiol; EMG: electromyography; MAS: modified Ashworth scale; MS: multiple sclerosis; N/A: not applicable; NRS: numeric rating scale; RCT: randomized controlled trial; TTF: time to treatment failure; THC: Δ^9-tetrahydrocannabinol

[b]: study sponsored by pharmaceutical company

[c]: author affiliation with pharmaceutical company

3.3 Bladder

Bladder dysfunction was assessed in four studies (Table 3.6).[54–57] Two of these studies were good quality RCTs, and two were poor quality observational studies. One good quality RCT comparing dronabinol (2.5mg THC), oral *Cannabis* extract (2:1 THC:CBD), and placebo on urinary incontinence, found a significant decrease in daily incontinence episodes for both *Cannabis* extract and THC.[56] One good quality study found no significant change in daily incontinence episodes with nabiximols (Sativex) use.[57] Adverse events were generally well-tolerated, with dizziness being commonly reported.

Table 3.6. Bladder assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Freeman et al. 2006[56]	RCT	14 weeks	Aged 18–64 years with clinically definite or laboratory-supported multiple sclerosis who, in the opinion of the treating doctor, had had stable disease for the previous 6 months, with Ashworth score of 2 in two or more lower limb muscle groups. Stabilise factors affecting spasticity were not altered 30 days before start of treatment. No ischaemic heart disease, active sources of infection, immunisations associated with foreign travel during the study, and medications such beta interferon, which could affect spasticity. No fixed-tendon contractures, severe cognitive impairment, past history of psychotic illness, major illness in another body area, pregnancy, use of THC at any time, and use of cannabis in the 30 days before the start of the study.	Reduction in UIE, as judged by the 3-day diary entry at BL and 13 weeks	Dronabinol (Marinol) (n=216) *Cannabis* extract (Cannador), (n=219; maximum possible dose of 25 mg daily depending on body weight	Placebo (n=222)	Change from BL: CE: 0.616 (38%) THC: 0.666 (33%) Placebo: 0.822 (18%) All showed a significant improvement ($p<0.01$) Cannabis extract showed a 25% improvement, and THC showed a 19% improvement relative to placebo. CE: p=0.005 THC: p =0.039	UTIs in all three groups; the drug was well tolerated overall	Good (23)
Kavia et al. 2010[57b]	RCT	69 days	MS with symptoms of OAB who fail to respond adequately to first-line therapies, stable dose of	Change in the number of incontinence episodes from baseline to	Nabiximols (Sativex) (n=67) Maximum dose of 8 sprays/3	Placebo (n=68) Mean dose of 17.05 sprays/day	Number of incontinence episodes/day	Most AEs were considered mild or moderate in	Good (25)

Table 3.6. Bladder assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			anticholinergic medication for at least 14 days prior to study entry and during the study, and at least three incontinence episodes over five consecutive days during the baseline period. No presence of urinary tract infection or any other known cause for detrusor overactivity, performing intermittent self-catheterization, history of use of cannabis or cannabis-derived medicines (street cannabis, dronabinol or nabilone) within 7 days of study entry, hypersensitivity to cannabinoids, a history of major psychiatric disorder (other than depression associated with underlying condition), severe personality disorder or history of substance abuse, severe cardiovascular disorder, history of epilepsy or significant renal or hepatic impairment, and concomitant use of fentanyl, levodopa, or sildenafil citrate.	end of treatment (last available data from weeks 7–8)	hours and 48 sprays/day Mean dose of of 8.91 sprays/day		Sativex: mean change from BL: -1.08 Placebo: mean change from BL: -0.98 p=0.569	severity; many were possible CNS-type events. Dizziness was a main AE.	
Maniscalco et al. 2018[54c]	Observational	4 weeks	Subjects with MS (revised McDonald's	Change in the OABSS scale	Nabiximols (Sativex) (n=18)	N/A	Improvement in median OABSS:	Only one patient	Poor (13)

Table 3.6. Bladder assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			criteria) with NRS score ≥ 4, failure to respond adequately to first-line antispastic treatments and who fulfill the requirements for THC/CBD oromucosal spray as add-on medication. Have at least 6 points at OABSS, refractory to conventional anticholinergic therapy carried out for at least 3 months. No presence of symptomatic urinary tract infection, intermittent self-catheterization, presence of LUTDs due to other conditions, history of use of herbal cannabis in 7 days prior to study entry, use of anticholinergic or alpha-blocker drugs for urinary symptoms, history of diabetes, cerebrovascular disease, or neurological disease other than MS, severe cardiovascular disorder and significant renal and/or hepatic impairment, pregnancy	from baseline to end of follow-up period (4 weeks).	Maximum dose of 12 sprays/day Mean dose of 3.8 sprays/day		BL: 17 4 weeks: 12 p=0.001	experienced mild dizziness	
Brady et al. 2004[55]	Open-label pilot study	16 weeks (8 weeks of 2.5 mg THC and CBD per	18-65 with advanced MS (Kurtzke > 6.5) and troublesome LUTS refractory to	Change in voided urine volumes (functional	Nabiximols (Sativex) and THC-only spray (n=21)	N/A	No significant improvement from baseline after eight weeks'	There were symptoms of intoxication (mild	Poor (11)

Table 3.6. Bladder assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
		spray and 8 weeks of 2.5 mg THC only)	conventional treatment. Detrusor overactivity proven on cystometry and a Mini-Mental State Examination 12 score > 27. Patients using street cannabis were required to stop four weeks prior to and during the study and urine tests for cannabis were carried out prior to recruitment. No detrusor failure, an indwelling catheter or inability to fulfil the requirements of the study protocol.	bladder capacity) after 8 weeks of treatment	Maximum dose of 48 sprays/day Mean dose of 33.7 mg/day (Sativex) and 31.2 mg/day (THC only). Significantly less THC-only treatment taken than THC/CBD treatment ($p<0.05$)		treatment with either THC/CBD or THC-only	drowsiness, disorientation and altered time perception) during titration	

AE: adverse event; BL: baseline; CBD: cannabidiol; CE: *Cannabis* extract; CNS: central nervous system; LUTD: lower urinary tract dysfunctions; LUTS: lower urinary tract symptoms; MS: multiple sclerosis; N/A: not applicable; NRS: numeric rating scale; OAB: overactive bladder; OABSS: overactive bladder symptom score; RCT: randomized controlled trial; THC: Δ^9-tetrahydrocannabinol; UIE: urinary incontinence episode; UTI: urinary tract infection

[b]: study sponsored by pharmaceutical company

[c]: author affiliation with pharmaceutical company

3.4 Pain

Pain was assessed in eight studies,[67,70,226,237,253,275,280,281] and included one article evaluating muscle stiffness.[70] Six studies were RCTs and two were observational studies. Six studies were good quality, one was fair quality, and one was poor quality. Four studies used nabiximols, two used dronabinol (2.5mg THC), one used nabilone (0.5mg or 1mg THC) in conjunction with gabapentin, and one used Cannabis extract (0.8-1.8 mg CBD:2.5 mg THC). Four good quality studies found CBM to have a beneficial effect on MS-related pain.

3.4.1 Studies Assessed with the Visual Analogue Scale

The Visual Analogue Scale (VAS) as an assessment for pain was evaluated in two studies,[253,281] one RCT and one observational study (Table 3.7). VAS pain scores showed a significant decrease with the use of nabilone and gabapentin combined, compared to placebo, in one good quality RCT.[281] Dizziness was a common adverse event in both studies.

3.4.2 Studies Assessed with the Numerical Rating Scale

The Numerical Rating Scale (NRS) was used to assess CBM for pain in five studies (Table 3.8).[67,226,237,275,280] There was a significant reduction in NRS score with dronabinol treatment in one good quality RCT.[67] Additionally, nabiximols (Sativex) use resulted in a decrease in NRS score in one good quality RCT[226] and in a fair quality observational trial.[275] Two good quality studies, one utilizing nabiximols (Sativex)[237] and one utilizing dronabinol,[280] found no significant decrease in NRS score. Dizziness, dry mouth, nausea, and tiredness were common adverse events.

3.4.3 Studies Assessed with the Category Rating Scale

The category rating scale (CRS) was used to evaluate muscle stiffness before and after *Cannabis* extract (Cannador) treatment in one good quality study (Table 3.9).[70] *Cannabis* extract was more effective than placebo at providing relief after 12 weeks of treatment. Common adverse events included dizziness, dry mouth and fatigue.

Table 3.7. Pain assessment with visual analogue scale

Reference	Study Design	Intervention Length	Study Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Turcotte et al. 2015[281b]	RCT	9 weeks	MS-induced NPP, RRMS (defined by 2005 McDonald criteria) and a score of 4 as per DN4 criteria. Age 18–65 years old; EDSS score of <6.5, VAS pain score for NPP symptoms 50, with pain symptoms present for at least 3 months; and current NPP treatment with GBP that is not effective at a stabilized dose of 1,800 mg daily for at least 1 month. No pregnancy or breastfeeding, history of alcohol or substance abuse, past or current nonpsychotic/psychotic emotional disorders, significant renal or hepatic insufficiency, cardiovascular disease (i.e., heart failure, cardiac arrhythmias) or uncontrolled hypertension, hypersensitivity to nabilone or its derivatives, and current reported use of CBs and/or related products; subjects with other possible confounding causes of neuropathies (i.e., diabetes, HIV, etc.)	Average change in VAS score after 9 weeks treatment	Gabapentin (≥ 1800 mg/day) and Nabilone (Cesamet; 0.5 or 1 mg capsules of nabilone; final dose of 1 mg given twice a day) (n=8)	Placebo (n=7)	Improvement in VAS pain intensity was greater, on average, in the nabilone vs placebo study group. This significant difference was maintained during both the titration and maintenance phases of the follow-up period ($p<0.01$)	Dizziness (62.5%), drowsiness, and dry mouth (50%). No serious adverse events were reported	Good (24)
Centonze et al. 2009[253]	Observational	6 weeks	Subjects with CNP (a constant or intermittent sensory symptom with unpleasant feelings or pain, lasting for more than 1 month and having a stereotyped neurological distribution and superficial localization) refractory or intolerant to	Mean reduction in pain (as measured by the VAS) after 3 weeks of treatment	Nabiximols (Sativex) (n=20) Maximum dose of 40 sprays/day	N/A	No significant effect over time was observed in mean VAS for pain. The mean VAS score for pain relief was	Sedation, dizziness, and nausea were the most frequently reported AEs	Poor (6)

Table 3.7. Pain assessment with visual analogue scale

Reference	Study Design	Intervention Length	Study Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			commonly prescribed medications. Concomitant medications and therapies were maintained during the study. No psychosis, substance abuse, cardiovascular disorders, and pregnancy.				particularly low after 3 weeks of treatment.		

AE: adverse event; CB: cannabinoid; CNP: central neuropathic pain; DN4: Douleur Neuropathique 4; EDSS: expanded disability status scale; GBP: gabapentin; HIV: human immunodeficiency viruses; MS: multiple sclerosis; N/A: not applicable; NPP: neuropathic pain; RCT: randomized controlled trial; RRMS: relapsing remitting multiple sclerosis; VAS: visual analogue scale

[b]: study sponsored by pharmaceutical company

Table 3.8. Pain assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Svendsen et al. 2004[67b]	Randomised double blind placebo controlled cross over trial	3 weeks	Age 18-55 years, and central pain at the maximal pain site with a pain NRS score >3. Central pain is pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside or with quantitative sensory testing, corresponding to at least one lesion in the central nervous system. Concurrent spasm related pain or other pain was allowed if the patient was able to distinguish it from central pain. No subjects who had used marihuana within the last three months. Subjects were not allowed to use marihuana during the study period.	Median spontaneous pain intensity (NRS score) in the last week of treatment	Dronabinol (Marinol) (n=24) Maximum dose of 10 mg THC/day Mean dose of 62 capsules over treatment period	Placebo Mean dose of 66 capsules over treatment period	Median spontaneous pain intensity during the last week of treatment was significantly improved during dronabinol treatment (4.0) than placebo (5.0) p=0.02	Most common AEs: CNS (dizziness, headache, tiredness), and the musculoskeletal system (myalgia, muscle weakness)	Good (27)
Rog et al. 2005[226c]	RCT	4 weeks	Subjects with MS for at least 6 months, central pain of at least 3 months' duration for which a nociceptive cause appeared unlikely and expected to remain otherwise stable during the study. A stable neuropathic pain medication regimen was maintained during the 2 weeks immediately before screening and throughout the study. Changes in medications or procedures expected to affect central MS pain were prohibited. No subjects with chronic visceral pain, headache,	Reduction in NRS-11 total pain scores from baseline to week 4 of treatment	Nabiximols (Sativex) (n=34) Maximum dose of 48 sprays/day Mean dose of 9.6 sprays/day	Placebo (n=32) Mean dose of 19.1 sprays/day	CBM: BL: 6.58, week 4: 3.85 Placebo: BL: 6.37, week 4: 4.96 Mean treatment difference CBM-placebo: -1.25 p= 0.005	Dizziness, dry mouth 88.2% of subjects on CBM developed at least one AE, compared with 68.8% on placebo	Good (27)

Table 3.8. Pain assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			spasticity-associated aching pain, secondary entrapment syndromes, or acute MS-related pain. Patients were excluded if their sensations were not subjectively deemed painful or if they had spasticity or painless spasms alone or another noncentral pain mechanism was considered more likely. Patients taking TCAs were required to take a maximum dose of 75 mg/day. No Cannabinoid/*Cannabis* use at least 7 days before screening or during the study was permitted. No history of major psychiatric disorder (other than depression associated with their underlying condition), severe concomitant illness, seizures, history or suspicion of substance abuse, concomitant severe nonneuropathic pain or the presence of illness such as diabetes mellitus, or scheduled procedures requiring general anesthesia during the study. Patients were also excluded if they were pregnant, lactating, taking levodopa therapy.						
Langford et al. 2013[237b]	RCT	98 days	CNP due to MS, for at least 3 months with a sum score of at least 24 on a pain 0–10 point NRS on the last 6 days during the baseline period.	The primary efficacy endpoint for was the response to	Nabiximols (Sativex) (n=167)	Placebo (n=172) Mean dose of 11.1 sprays/day	The number of responders at the 30 % improvement level in mean	AEs with severe intensity were observed most often in the nervous system	Good (26)

Table 3.8. Pain assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			Analgesic regimen stable for at least 2 weeks preceding the study entry day. Subjects were required to have had an average of three or more sprays of THC/CBD per day in the 7 days prior to completion of phase A, shown tolerability to the study medication, and maintained a stable treatment regimen throughout the study for all neuropathic pain medications. No severe pain from other concomitant conditions, pain that was not of a central neuropathic origin that would interfere with the patient's assessment of neuropathic pain due to MS, patients with a history of significant psychiatric (other than depression associated with their underlying condition), renal, hepatic, cardiovascular, or convulsive disorders, or with a sensitivity to cannabis or cannabinoids, participants who had experienced an adverse event in phase A were also excluded from phase B.	treatment, defined as an improvement of 30 % or more in patient's mean pain NRS score from baseline to the last week of treatment (98 days)	Maximum dose of 12 sprays/day Mean dose of 8.8 sprays/day		pain NRS score in the last week of treatment totaled 50% in the THC/CBD spray group compared to 45% in the placebo group p= 0.234	disorders, gastrointestinal system disorders, and psychiatric system disorders. 75% in treatment group and 62% in placebo group experienced AEs. Common AEs: vertigo, nausea, dry mouth, dizziness, somnolence	
Schimrigk et al. 2017[280c]	RCT followed by long-term follow-up	16 weeks RCT	Aged 18–70 years, stable disease symptoms and moderate to severe CNP (NRS ≥4) at maximal pain area for at least 3 months as reported by patients.	Mean change of pain intensity (NRS) from baseline to	Dronabinol (Marinol) (n=124) 2.5 mg/capsule	Placebo (n=116)	Mean change of pain intensity (NRS pain) of dronabinol was 1.92 and	Double-blind and open-label period 92.9% of patients experienced at least one AE.	Good (23)

Table 3.8. Pain assessment with numerical rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			No peripheral pain syndromes, pre-existing psychotic disorders, severe cardiac diseases, or known substance abuse. Continuing therapy with amitriptyline and gabapentin, if started at least 3 months ago with a stable dose and oral intake of tramadol as rescue medication for acute pain attacks, was allowed.	mean of weeks 1–16	daily dose between 7.5-15 mg Mean dose of 12.7 mg/day		placebo was 1.81 p=0.6760	Dizziness, vertigo, fatigue, dry mouth, nausea	
Turri et al. 2018[275]	Observational	1 month	MS according to Polman criteria, presence of chronic pain, spasticity recalcitrant to other drugs, age 18-65. No modification of ongoing therapy within the past 3 months; relapses in the 6 months prior to and during the study; high-dosage steroids in the last 6 months; pregnancy; severe kidney/liver disease; and history of drug abuse or mental disorder.	NRS score for pain before and after 1 month of therapy	Nabiximols (Sativex) (n=28) Mean dose of 6.9 sprays/day	N/A	A significant improvement in NRS score after drug therapy (6.61 at BL to 3.55 after 1 month). p= 0.0001	dizziness: 4 drowsiness: 2 lack of concentration: 2	Fair (16)

AE: adverse event; BL: baseline; CBD: cannabidiol; CBM: cannabis-based medicine; CNP: central neuropathic pain; CNS: central nervous system; MS: multiple sclerosis; N/A: not applicable; NRS: numeric rating scale; RCT: randomized controlled trial; TCA: tricyclic antidepressant; THC: Δ^9-tetrahydrocannabinol

[b]: study sponsored by pharmaceutical company

[c]: author affiliation with pharmaceutical company

Table 3.9. Pain assessment with category rating scale

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Zajiceck et al. 2012[70c]	RCT	12 weeks	Ages 18-64 years, stable disease for the previous 6 months and troublesome and current score of at least 4 on an 11 point CRS. All physiotherapy regimens or medications likely to affect spasticity were not altered in the 30 days before study start. No active sources of infection or immunomodulatory drugs that might affect spasticity, fixed tendon contractures, severe cognitive impairment, history of psychosis, major illness, pregnancy and cannabis use in the 30 days before study start.	CRS to measure perceived change in muscle stiffness after 12 weeks of treatment	*Cannabis* extract (Cannador) (n=144) Maximum dose of 25 mg/day At the end of the study, 24.5% were taking the highest dose	Placebo (n=135) 69.4% were taking the highest dose (25 mg/day)	The proportion of patients with self-reported relief, at week 12, (defined as categories 0-3 on the CRS) was 29.4% in the CE group and 15.7% in the placebo group p=0.004	Common AEs: dizziness, dry mouth, fatigue, UTI, headache, asthenia.	Good (26)

AE: adverse event; CE: *Cannabis* extract; CRS: category rating scale; MS: multiple sclerosis; RCT: randomized controlled trial; UTI: urinary tract infection

[c]: author affiliation with pharmaceutical company

3.5 Cognition

Cognition was assessed in six studies[58,81,276,285–287] (Tables 3.10 and 3.11). Two RCTs, evaluating nabiximols (Sativex); and four observational studies, evaluating dried *Cannabis*. Three studies were poor quality, one was fair quality, and two were good quality. The observational studies provided little, if any, information regarding intervention length or adverse events; since dry *Cannabis* was used, dosing and formulation were not reported.

3.5.1 Studies Assessed with other cognition outcome measures

The effect of dry *Cannabis* on Diagnostic and Statistical Manual of mental disorders (DSM-IV) diagnosis in MS patients[81] and on the 10/36 spatial recall test[60] was assessed in poor quality observational studies (Table 3.10). Adverse events were not reported in either study.

3.5.2 Studies assessed with the Paced Auditory Serial Addition Test (PASAT)

Four studies [58,276,285,286] evaluated CBM use and the Paced Auditory Serial Addition Test (PASAT) (Table 3.11). Two good quality RCTs utilizing nabiximols (Sativex)[58,276] found no significant change in PASAT score between treatment and placebo groups. Adverse events were reported in only the RCTs; dizziness, fatigue, mouth discomfort, and drowsiness were commonly reported.

Table 3.10. Cognition assessment (other)

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Ghaffar & Feinstein 2008[81]	Observational	Ninety-five subjects (67.9%) denied having ever used illicit drugs. Thirty-two subjects (22.9%) had used cannabis at least once in their lives. Ten subjects (7.7%) were defined as current cannabis users based on use within the last month.	Community dwelling patients with MS attending an outpatient MS clinic in Toronto, Ontario, Canada, were enrolled in the study	Cognitive function in MS	Smoked *Cannabis* (n=10) A single use ranged in amount from one-quarter to one marijuana cigarette Time of last *Cannabis* use was 1 to 30 days before testing	Control group (MS subjects who do not use *Cannabis*) (n=130)	No difference between *Cannabis* users and controls on any individual DSM-IV diagnostic category. The proportion of patients meeting DSM-IV criteria for a psychiatric diagnosis was higher in cannabis users (90%) vs non cannabis users (55%) p=0.04	Not reported	Poor (14)
Pavisian et al. 2015[287c]	Observational	*Cannabis* group were daily users	Right-handed individuals, age 18-60 years, normal or corrected-to-normal vision. No history of brain injury, illicit drug use other than cannabis, alcohol abuse, concurrent neurologic diseases, treatment with steroids in the past 3 months, neuropsychological testing in the past year, claustrophobia, mental handicap, and psychosis.	10/36 spatial recall test	Smoked *Cannabis* (n=20) Participants instructed not to smoke 24 hours prior to testing	Control group (*Cannabis* naïve MS subjects) (n=19)	Cannabis smokers were more impaired on the 10/36 Spatial Recall Test *Cannabis* mean: 16.40 Non-*Cannabis* mean: 20.79 p=0.03	Not reported	Poor (13)

DSM-IV: diagnostic and statistical manual of mental disorders; MS: multiple sclerosis

[c]: author affiliation with pharmaceutical company

Table 3.11. Cognition assessment with paced auditory serial addition test

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Aragona et al. 2009[58]	Randomised, double-blind, placebo-controlled, crossover trial	3 weeks	18 and 60 years of age, right-handed with normal right-hand function; a baseline EDSS 18 score ranging from 3.5 to 6.5; a stable disease for at least 30 days before study entry and no systemic corticosteroid therapy within 4 weeks of randomization; significant spasticity in at least 2 muscle groups; antispastic and immunomodulatory agents stable, before the study entry, for at least 1 and 6 months, respectively; no history of epilepsy of alcohol or substance abuse and no major medical illnesses; no psychiatric disorders or cognitive impairment at first evaluation; no history of psychiatric disorders; no concomitant therapy with psychoactive drugs; no female patient who was pregnant, lactating, or planning pregnancy during the course of the study; and no	Change in PASAT score after three weeks of treatment	Nabiximols (Sativex) (n=17) Mean dose of 8.2 sprays/day	Placebo Mean dose of 15.16 sprays/day	No significant change found in PASAT score in placebo (mean 43) vs Sativex (mean 42.3) p=0.79	Generally mild. Most common adverse events on treatment; mouth dryness and burning, fatigue, drowsiness, slow thinking.	Good (22)

Table 3.11. Cognition assessment with paced auditory serial addition test

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			previous use of cannabis.						
Vachova et al. 2013[276b]	RCT	48 weeks	MS of any subtype, at least moderate levels of MS spasticity not wholly relieved with current anti-spasticity therapy; be on a stable medication regimen (i.e., not changed in the last three months or four weeks for disease-modifying or anti-spasticity/cognition medications, respectively); be willing to abstain from alternative cannabinoid use for 30 days prior to screening and throughout the study. No current or past history of drug or alcohol abuse or significant psychiatric illness, other than depression associated with MS, hypersensitivity to cannabinoids; subjects pregnant, lactating or planning pregnancy; had received an investigational medicinal product within 12 weeks of screening; had any concomitant disorders	Mean change from baseline to end of treatment in PASAT	Nabiximols (Sativex) (n=62) Maximum dose of 12 sprays/day Mean dose of 6.4 sprays/day	Placebo (n=59) Mean dose of 10 sprays/day	The adjusted mean PASAT total score improved by 6.02 points in the Sativex group, compared with an adjusted improvement of 7.49 points in the placebo group.	62.9% of subjects in the Sativex group and 32.2% of subjects in the placebo group experienced AEs. The most common AEs in Sativex patients were, vertigo (9.7%), fatigue (8.1%), and dizziness (8.1%). 8.1% in the Sativex group developed at least one SAE, while there were no SAEs reported in the placebo group.	Good (26)

Table 3.11. Cognition assessment with paced auditory serial addition test

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			or abnormalities that could either put the patient at risk, affect the patient's ability to participate or influence the result of the study.						
Honarmand et al. 2011[285c]	Observational	Average age at onset of cannabis use was 17.0 years (median 15.0) and the average duration of cannabis use was 26.6 years (median 31.0) Eight subjects (32.0%) re-ported using cannabis for medicinal reasons, 3 (12.0%) for recreational reasons, and 14 (56.0%) for a combination.	Cannabis Sample: Subjects (18-65) who used cannabis recently and whose urine tested positive for cannabinoids only (no other illicit drugs) on the day of assessment were included; subjects who reported cannabis use less than 12 hours prior to testing were excluded. No history of traumatic brain injury, psychotic illness, concurrent neurologic diseases, and poor visual acuity (less than 20/70 corrected, both eyes). No subjects who had undergone neuropsychological testing within the last year. Control Sample: cannabis-naïve subjects with MS; urine that tested negative for cannabinoids and	Effects on cognitive function in those with MS, measured by 3-second PASAT	Dried *Cannabis* (n=25) Inhalation (smoking/vaporization): 24 Eating: 1 72.0% used cannabis on a daily basis, 24.0% weekly, and 4.0% biweekly	Control group (MS subjects with no recent history of *Cannabis* use) (n=25)	*Cannabis* users scored significantly lower on the PASAT 3.0 compared to the non-*Cannabis* group *Cannabis:* 36.0 Non-*Cannabis*: 44.0 p=0.02	Not reported	Poor (14)

Table 3.11. Cognition assessment with paced auditory serial addition test

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			other illicit drugs. A remote history of occasional teenage use was not an exclusionary factor.						
Pavisian et al. 2014[286c]	Observational	Daily (n=17), 4-5 times/week (n=2), 2-3 times a week (n=1)	18-60 years of age. No history of brain injury, illicit drug use other than cannabis, alcohol abuse, concurrent neurologic diseases, treatment with steroids in the past 3 months, neuropsychological testing in the past year, claustrophobia, mental handicap, and psychosis. All subjects had normal or corrected-to-normal vision. Cannabis group: Subjects who regularly used cannabis and whose urine tested positive for cannabis metabolites only were enrolled. Control sample: Subjects with MS who had never used cannabis were group-matched to the cannabis group on demographic and disease-related variables. All control	Performance on the 2-second PASAT tasks	Smoked *Cannabis* (n=20) Daily (n=17), 4 to 5 times a week (n=2), and 2 to 3 times a week (n=1)	Control group (*Cannabis* naïve MS subjects) (n=19)	The *Cannabis* group performed more poorly on the PASAT compared to the non-*Cannabis* group *Cannabis*: 28.35 Non-*Cannabis*: 39.47 p=0.02	Not reported	Fair (15)

Table 3.11. Cognition assessment with paced auditory serial addition test

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			subjects had negative urine and saliva tests.						

AE: adverse event; EDSS: expanded disability status scale; MS: multiple sclerosis; PASAT: paced auditory serial addition test; RCT: randomized controlled trial; SAE: serious adverse event

[b]: study sponsored by pharmaceutical company

[c]: author affiliation with pharmaceutical company

3.6 Balance and Walking

Three studies evaluated the use of CBM for balance/walking (Table 3.12).[77,252,284] Interventions included nabiximols (Sativex) and smoked 1.54% THC *Cannabis* cigarettes. All studies were poor quality and indicated that CBM use results in impaired balance but faster walking speed. A comprehensive list of adverse events was not provided in any of the three studies; one study reported reasons for discontinuation of nabiximols to be drowsiness and confusion.

Table 3.12. Balance and walking assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Greenberg et al. 1994[284]	RCT	1 day marijuana cigarette 1 day placebo	MS by clinical and laboratory criteria with the predominant clinical deficit a spastic myelopathy; stiff-legged gait with circumduction of at least one leg. No cardiac, rheumatologic, or neurologic disease.	Dynamic posturography before and after smoking *Cannabis*	*Cannabis* (1.54% THC) or alcohol-extracted *Cannabis* placebo MS Subjects (n=10)	Normal controls (n=10)	Noise Variance: Patients: Pre smoking EO: 1.02 Pre smoking EC: 4.83 Placebo EO: 0.72 Placebo EC: 3.27 *Cannabis* EO: 1.67 *Cannabis* EC: 5.37 Normal Controls: Presmoking EO: 0.59 Presmoking EC: 1.93 Placebo EO: 0.59 Placebo EC: 3.20 *Cannabis* EO: 0.79 *Cannabis* EC: 2.80 *Cannabis* smoking significantly decreased postural control, with EO and EC, in patients and normal controls, as measured by noise variance p=0.0025	Not reported	Poor (10)
Coghe et al. 2015[77c]	Observational	1 month	Ability to walk for at least 6 m regardless of the use of aids and the ability to take nabiximols according to medical judgment and the Italian Drugs Agency criteria. All patients were non-responders to previous spasticity treatments.	Walking speed changes before and after 1 month of treatment	Nabiximols (Sativex) (n=20) Mean dose of 5.6 sprays/day	N/A	The patients exhibited improved speed (BL = 0.43, 1 month = 0.49; m/sec) p<0.001	Not reported	Poor (13)
Castelli et al. 2019[252c]	Observational	12 months	≥18 years; NRS score ≥ 4, lack of response to common and ongoing antispastic drugs;	The postural sway (mm) without cognitive task	Nabiximols (Sativex) (n=22)	N/A	There was impaired postural control in single-task conditions	Drowsiness and confusion lead to withdrawal	Poor (14)

Table 3.12. Balance and walking assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			negative pregnancy test; absence of concomitant severe cardiovascular illnesses; no prior or current psychiatric diseases; no current use of street cannabis and/ or other psychoactive drugs.	interference after 12 months of Sativex use	Median dose of 6 sprays/day		with continued CBM use p=0.044		

BL: baseline; EC: eyes closed; EO: eyes open; MS: multiple sclerosis; N/A: not applicable; NRS: numerical rating scale; RCT: randomized controlled trial; THC: Δ^9-tetrahydrocannabinol
[c]: author affiliation with pharmaceutical company

3.7 Tremor

One RCT study[62] of good quality evaluated the use of *Cannabis* extract (2:1 THC:CBD) for MS-related tremor (Table 3.13). No statistical difference was observed between the Cannador and placebo groups. Adverse events included drowsiness and light-headedness and were mild and well-tolerated.

3.8 Safety

Six studies[236,251,260,267,271,278] had a primary outcome involving general adverse events (AEs) and/or safety (Table 3.14). Three studies were fair quality and three were poor quality, and all but one was observational. Five studies utilized nabiximols (Sativex), and one utilized dronabinol (2.5mg THC) and oral *Cannabis* extract (4:1 THC:CBD). Adverse events were mild to moderate and well tolerated; common AEs were dizziness, nausea, oral discomfort, and fatigue.

Table 3.13. Tremor assessment with tremor index

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Fox et al. 2004[62]	Randomised controlled double-blind crossover study	2 weeks	Diagnosis of definite MS (Poser criteria); 18-64 years of age; visible upper limb tremor No cognitive impairment; history of ischemic heart disease or psychotic illness.	Reduction in TI after 2 weeks of Cannador treatment	*Cannabis* extract (Cannador) Maximum dose of 0.125 mg/kg THC twice daily (n=14) Mean dose of 0.107mg/kg twice a day	Placebo Mean dose equivalent of 0.123mg/kg twice a day	The effect of treatment size was 0.45 and there was no difference between the two groups. p=0.55	AEs were mild; 10 patients reported AEs on treatment; 2 on placebo Most common AEs: drowsiness, light-headedness, memory disturbance, dysphoria, euphoria, increased appetite, dry mouth	Good (22)

AE: adverse event; MS: multiple sclerosis; THC: Δ^9-tetrahydrocannabinol; TI: tremor index

Table 3.14. Safety assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Killestein et al. 2002[251]	Randomised, double-blind, placebo-controlled, crossover study	4 weeks	PPMS or SPMS, disease duration 1 year, mean Ashworth spasticity score of 2 or more in at least one limb during screening, EDSS score between 4 and 7.5. No other disease of clinical importance, use of other investigational drug, disease exacerbation, steroid treatment or use of cannabinoids in the 2 months preceding study entry, and history of substance abuse, depression, psychosis, or schizophrenia.	Safety, and tolerability of THC and plant-extract capsules after 4 weeks of treatment	Dronabinol (Marinol) and *Cannabis* extract (Cannador) (n=16) Ideally 10mg/day THC by the end of the study	Placebo	No serious AEs emerged. AEs were more common during plant-extract treatment (41) compared with placebo treatment (20) (p= 0.01), but there was no difference between THC (20) and placebo (20)	Most AEs were rated as mild.	Fair (17)
Wade et al. 2006[278b]	Long-term open label study	Mean duration was 434 days for patients remaining on treatment and 225 for patients who stopped	MS of any type, with at least one of the following symptoms: spasticity, spasms, bladder-related problems, tremor or pain that was not obviously musculoskeletal with severity recorded as >/=50 mm on a 100-mm VAS. No current or past history of drug or alcohol abuse, significant psychiatric illness other than depression associated with MS, serious cardiovascular	Safety of treatment as measured by AEs after long-term Sativex use	Nabiximols (Sativex) (n=137) Maximum dose of 48 sprays/day Mean dose of 11 sprays/day	N/A	137 patients reported a total of 292 unwanted effects, of which 251 (86%) were of mild to moderate intensity.	Oral pain, dizziness, diarrhea, nausea, oral mucosal disorder and dry mouth	Poor (13)

Table 3.14. Safety assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			disorder, significant renal or hepatic impairment or a history of epilepsy.						
Rog et al. 2007[267b]	Open-label extension trial	Indefinite duration: About 2 years	Adult patients with CNP syndromes associated with MS, as defined by the Poser criteria. No history of major psychiatric disorder other than depression associated with their underlying condition; severe concomitant illness, seizures, history or suspicion of substance abuse; concomitant severe on neuropathic pain or the presence of illness such as diabetes mellitus; or scheduled procedures requiring general anesthesia during the study. No subjects who were pregnant, lactating, taking levodopa therapy within 7 days of study entry or had known or suspected hypersensitivity to cannabinoids	The number, frequency, and type of AEs reported	Nabiximols (Sativex) (n=63) Maximum dose of 48 sprays/day At 1 year of treatment: Mean dose of 7.5 sprays/day. In last six full days of treatment: Mean dose of 6.1 sprays/day	N/A	92% of subjects experienced a treatment-related AE. AEs were rated as mild (75%), moderate (78%), or severe (51%). AEs that led to 17 patients withdrawing from the trial were: nausea, weakness, dizziness, fatigue aggravated, feeling intoxicated, and vomiting, anorexia, ventricular bigeminy and circulatory collapse, oral discomfort, abnormal coordination, headache, impaired judgment, speech disorder, agitation, hallucination, and facial	Dizziness, balance impairment, nausea, feeling intoxicated	Fair (16)

Table 3.14. Safety assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
							swelling. Twelve SAEs occurred in 16%, 2 of which (ventricular bigeminy and circulatory collapse) were treatment related.		
Scully 2007[271]	Observational	At least 4 weeks	Subjects with MS using marijuana oromucosal spray as part of a UK trial on its efficacy in MS pain	Oral adverse events of Sativex	Nabiximols (Sativex) (n=9) Maximum dose of 48 sprays/day	N/A	8 subjects admitted to a stinging sensation on using the oromucosal cannabis spray 4 subjects had oral mucosal white lesions in the floor of mouth All lesions visibly resolved or decreased by a second visit	Not reported	Poor (6)
Serpell et al. 2013[236b]	Open label	Up to 3 years' exposure, mean duration of treatment exposure for all patients was 334 days (1 to 801 days)	≥18 years of age, haematology and blood biochemistry that was considered normal or clinically acceptable. No history of significant psychiatric, renal, hepatic, cardiovascular, convulsive or any other major disorder, terminally ill patients,	Safety and tolerability of long-term therapy with Sativex, which was determined by measuring the incidence, frequency and type of AEs	Nabiximols (Sativex) (n=146) Maximum dose of 8 sprays/3 hours and 48 sprays/day Mean dose of 10 sprays/day	N/A	The incidence of all-causality AEs in this study was 95%. Most AEs were considered mild/moderate in severity.	The most common all causality AEs were in the categories of 'CNS disorders', 'gastrointestinal disorders' and 'infections and infestations'. The most common treatment-related AEs by preferred	Fair (17)

Table 3.14. Safety assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			known hypersensitivity to the study medication or taking regular levodopa within 7 days of study entry; history of substance abuse; females of child-bearing potential or their partners (unless willing to ensure effective contraception); pregnant or lactating females or those planning pregnancy; subjects with any physical abnormality at screening; subjects intending to donate blood during the study; previous participated in this study.					term were 'dizziness', 'fatigue' and 'headache'.	
Oreja-Guevara et al. 2015[260b]	Observational	12 months	≥ 18 years with moderate or severe MS-related spasticity who had not responded adequately to other antispasticity medications and who were prescribed Sativex spray independently of a patient's potential participation in the study. At the treating physician's discretion, patients who did not meet study requirements were	Frequency of adverse events reported	Nabiximols (Sativex) (n=205) Mean dose of 6.6 sprays/day	N/A	57 adverse events of mild (72%), moderate (16%) or severe (12%) intensity were reported by 41 patients (20% of the cohort) during the observation period.	GI (diarrhea, oral mucosa) nervous (dizziness, somnolence), and psychiatric systems (depression, confusion)	Poor (13)

Table 3.14. Safety assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
			excluded, or those with a medical or psychological disorder that would limit their ability to understand questions and complete the questionnaires.						

AE: adverse event; CNP: central neuropathic pain; CNS: central nervous system; EDSS: expanded disability status scale; GI: gastrointestinal; MS: multiple sclerosis; N/A: not applicable; PPMS: primary progressive MS; SAE: serious adverse event; SPMS: secondary progressive MS; THC: Δ^9-tetrahydrocannabinol; VAS: visual analogue scale

[b]: study sponsored by pharmaceutical company

3.9 General Symptoms

Two studies,[82,256] one RCT of good quality and one observational study of poor quality, had no specific symptom measure, and therefore assessed general symptom management of nabiximols (Sativex) (Table 3.15). There was no significant difference between placebo and nabiximols (Sativex) for treating the primary symptom score (PSS) in a good quality RCT.[82] The most commonly reported adverse events were dizziness and fatigue.

Table 3.15. General symptom assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Wade et al. 2004[82b]	RCT	6 weeks	Stable over the preceding four weeks (no relapse), medication not changed in the last four weeks; be willing to abstain from alternative cannabinoid use for seven days prior to screening and throughout the study; volunteer one of the five target symptoms at a sufficient level of severity (spasticity, spasms, bladder problems, tremor or pain that was not obviously musculoskeletal). No current or past history of drug or alcohol abuse; significant psychiatric illness other than depression associated with MS; serious cardiovascular disorder; significant renal or hepatic impairment or history of epilepsy; planned visit abroad during the active study. Caution was exercised for patients taking drugs metabolized by certain cytochrome P450 enzymes (TCAs and anticonvulsants).	PSS: VAS score for each patient's most troublesome symptom with 6 weeks of Sativex use	Nabiximols (Sativex) (n=80) Maximum dose of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in 3 hours	Placebo (n=80)	The PSS for the active group (-25.2) and placebo group (-19.35) did not have a significant difference (-5.93) p=0.124	Dizziness, disturbance of attention, headache, fatigue, somnolence, disorientation, feeling drunk, vertigo, application site discomfort, nausea, diarrhea, mouth ulceration	Good (26)

Table 3.15. General symptom assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Etges et al. 2016[256][b]	Observational	Duration of exposure ranged from 1 to 4283 days (mean of 954 days)	Patients prescribed Sativex in the UK, Germany, and Switzerland	Prescribers perceived benefit during observation period	Nabiximols (Sativex) (n=941) Maximum dose of 12 sprays/day Mean dose of 5.4 sprays/day	N/A	83% of patients were receiving benefit in at least one DCP of 2-3 months, with 78% reporting benefit at every DCP.	Most commonly reported AEs: nervous system disorders (117 patients), psychiatric disorders (68 patients), GI disorders (57 patients) Most common treatment-related AEs: dizziness (22 patients), fatigue (16 patients)	Poor (10)

AE: adverse event; CBD: cannabidiol; DCP: data collection period; GI: gastrointestinal; MS: multiple sclerosis; N/A: not applicable; PSS: primary symptom score; RCT: randomized controlled trial; TCA: tricyclic antidepressant; THC: Δ^9-tetrahydrocannabinol; UK: United Kingdom; VAS: visual analogue scale

[b]: study sponsored by pharmaceutical company

3.10 Progression

The effect of dronabinol (Marinol) on MS disease progression was assessed in one RCT of good quality (Table 3.16)[279] using the expanded disability status scale (EDSS) score as a measure of progression. No statistically significant difference in EDSS score progression was seen between treatment and placebo groups. Adverse events (AEs) were similar between placebo and treatment groups in both quantity and quality. Common AEs included dizziness, fatigue, and balance impairment.

Table 3.16. Progression assessment

Reference	Study Design	Intervention Length	Cohort Characteristics	Primary Outcome	Intervention (n=)	Comparator (n=)	Results	Adverse Events	Quality Score (/28)
Zajicek et al. 2013[279]	RCT	36 months	18–65 years; PPMS or SPMS, evidence of disease progression in the preceding; an EDSS score of 4·0–6·5 at baseline; no cannabis use for the duration of the trial. No use of immunomodulatory/disease modifying therapies 12 months prior; systemic corticosteroid use in the previous 3 months; predominant relapsing-remitting disease in the previous 12 months; MS relapse in the previous 6 months that was likely to have affected patients' EDSS scores; history of previous psychosis or other serious medical illness; pregnancy; serious cognitive impairment; cannabinoid use within the previous 4 weeks.	Time to EDSS score progression of at least 1 point from a baseline EDSS score of 4.0, 4.5, or 5.0 or at least 0.5 points from a baseline EDSS score of 5.5 or greater (confirmed by a physician at the next scheduled 6 month visit)	Dronabinol (Marinol) (n=332) Maximum dose of 28 mg (8 capsules), depending on body weight and AEs	Placebo (n=166)	145 patients (44%) in the dronabinol group had EDSS score progression compared with 73 (44%) in the placebo group p= 0.57	35% patients on dronabinol had at least one serious AE compared with 28% of patients on placebo (most common being admission to hospital for MS-related issues). The median number of AEs were 11/person in the dronabinol group, and 10/person in the placebo group. Most common AEs: fatigue, dizziness, falls/injuries, mobility, balance and coordination problems, infections, muscle disorders (weakness, spasticity, stiffness, spasms or tremor), dissociative thinking or perception disorders, depression, aches and pains, constipation, diarrhea, fecal incontinence, joint disorders, UTIs	Good (27)

AE: adverse event; EDSS: expanded disability status scale; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; RCT: randomized controlled trial; SPMS: secondary progressive multiple sclerosis; UTI: urinary tract infection

CHAPTER 4: DISCUSSION

Multiple sclerosis is a disease where the use of alternative therapies is common. *Cannabis* and *Cannabis*-based medicine (CBM) have been available for treating some MS symptoms for several years. However, a better understanding of the potential role of CBM in MS is still needed.

A systematic search of the literature yielded 2756 articles, with 60 included in the final review. Most studies (n=37) evaluated the use of CBM for the treatment of MS spasticity and/or pain; other studied symptoms included cognition, bladder dysfunction, balance/walking, tremor, and an evaluation of safety/adverse events. The majority of included studies were observational in design and published since 2010. A variety of CBM products were evaluated, although nabiximols was the most commonly studied intervention. In general, the literature confirmed that CBM may benefit MS pain and spasticity, while highlighting the need for more, better quality research for other MS symptoms. Reported adverse effects were mild; however, more long-term studies are needed to accurately examine the potential adverse effects of CBM in MS, particularly as it relates to cognition.

Due to the high variability between studies, interpreting and comparing results of the current literature is a challenge. Substantial heterogeneity was due to variations in study populations, products and doses studied, length of interventions, outcome measures, and study quality. The most obvious variation between study populations was related to prior *Cannabis* use and MS phenotype. Prior *Cannabis* use was not consistent between study cohorts and was not always reported. Some studies required subjects to have no *Cannabis* use anywhere from 7 days to three months prior to the study start, while others required *Cannabis*-naïve subjects. Few studies implemented urine testing[251] to evaluate cannabinoid use prior study start, or to ensure the placebo/comparator group was abstaining from cannabinoid use.[249,279] While past *Cannabis* use does not impact dose of nabiximols administered or incidence of adverse events,[288] it may impact long-term adverse events, such as cognition[289–291] and treatment effect.

The MS phenotype also varied between cohorts. Many studies indicated the need for participants to have a progressive form of the disease (either secondary progressive or primary progressive). However, long-term studies evaluating CBM's impact on disease progression

should include subjects with relapsing-remitting MS. The majority of current disease-modifying therapies are only indicated in relapsing disease because of their anti-inflammatory properties.[92] Since cannabinoids are immunomodulatory[154,157] it would seem feasible that they may also benefit individuals with relapsing MS.

Both synthetic and naturally derived cannabinoid products were evaluated, although nabiximols (Sativex) was the most commonly used therapy (n=40). Nabiximols is a prescription product with 2.7 mg THC: 2.5 mg CBD per spray. It is available in over 20 countries with an indication for MS spasticity and pain,[208,212] and many MS clinicians are familiar with its use.

There is value in administering THC and CBD together, because THC is used to reduce MS pain and spasticity,[142,143] whereas CBD counteracts the negative intoxicating effects of THC.[142,154,158] Nabiximols is also a naturally-derived product, which may be seen advantageous, as natural products are often presumed to have fewer and less serious adverse events.[224] However, it is still unknown which type of product, synthetic or natural derived, is best in a clinical setting.

The oromucosal administration of nabiximols allows THC and CBD to avoid first-pass metabolism before entering the systemic circulation.[292] This avoids the formation of the active metabolite 11-hydroxy-THC[137,178] which is present with oral administration.[137,178,189] Presence of 11-hydroxy-THC results in a more rapid onset of intense psychoactive effects compared to THC or *Cannabis*.[178,293,294] While smoking also avoids first-pass metabolism,[178] it can lead to respiratory issues[243,244] and is therefore not a desirable method of administration.

Nabiximols is self-titrated due to individual variations in tolerability. Maximum allowed doses in the included studies were inconsistent and ranged from 12 sprays/day (32 mg and 30 mg of THC and CBD, respectively) to 48 sprays/day (130 mg and 120 mg of THC and CBD, respectively). It is interesting to note that these higher doses are above the recommended maximum of 12 sprays/day.[295] Given that the mean number of sprays reported in the included studies was 6-7 in a 24-hour period, it is assumed that a dose of 48 sprays/day was rarely reached due to adverse effects. Self-titrated doses of the placebo comparator were consistently higher (up to 19.1 sprays/day[226]) than the active product.[45,57,255,262,276,58,62,67,70,82,226,237,254] Therefore, the maximum allowable dose for nabiximols may have been so high to allow for the increase self-administered placebo doses.

Other prescription products evaluated included oral synthetic cannabinoids (dronabinol, nabilone), and oral *Cannabis* extract formulations (Cannador). The maximum doses of oral synthetic THC products ranged from 2 mg/day[281] (nabilone, administered with gabapentin) to 28 mg/day[279] (dronabinol); *Cannabis* extract (Cannador) had a maximum daily dose of 30 mg/day THC.[225]

Street *Cannabis* was also evaluated in four studies, one of which indicated that most subjects that had consumed *Cannabis* for years, including prior to MS diagnosis.[285] The other three did not specify length of *Cannabis* use, however in all studies *Cannabis* was used at least biweekly. While those with MS may use street *Cannabis* to treat their symptoms, it is difficult to standardize key factors such as dose (ratio of CBD:THC, and other cannabinoids present in the *Cannabis*), smoking technique (breath hold, depth of inhale, etc.), and the duration of use.

Intervention length ranged from one day to three years, with most studies having a duration of exposure between one and three months. Beneficial effects of CBM, especially for spasticity, occur within the first four weeks of treatment.[255,258,265,296] If there is no effect in that time, the subject is unlikely to find relief with CBM.[255] Additionally, self-titrating doses typically plateau at around four weeks of treatment.[82] A trial of at least one month, then, would allow adequate time for a subject and his/her clinician to assess symptom response to CBM treatment. Longer durations of exposure are needed to evaluate adverse effects, such as memory or cognitive impairment, and to evaluate CBM on disease progression. Of the six studies assessing adverse effects/safety, four were at least 12 months long, and therefore more likely to identify long-term adverse events with regular CBM use. However, the RCTs evaluating cognitive function were only three weeks and four months in duration, arguably too short to accurately determine the impact of CBM on cognitive function longer term.

A variety of subjective and objective assessment measures were used by the studies included in this review. A Multiple Sclerosis Task Force associated with the Academy of Neurologic Physical Therapy reviewed 63 measures of MS symptoms. Ten measures were deemed “highly recommended” due to their psychometric properties, clinical utility, or both.[40,41] While these recommendations do not include any measures specifically for spasticity or pain, two self-reported questionnaires that assess overall well-being, the Multiple Sclerosis Quality of Life-54 (MSQOL-54), and the Multiple Sclerosis Impact Scale (MSIS-29) both address aspects

related to pain and/or spasticity.[40,78,79,297] Two of the most prominent assessment measures used by the included studies for pain and/or spasticity were the Ashworth/Modified Ashworth Scale (MAS) and the Numerical Rating Scale (NRS). The NRS, while not a highly recommended measure, is still considered valid and reliable for spasticity assessment, more so than the Ashworth scale.[43] The Ashworth and modified Ashworth scales were used as the primary assessment measure for spasticity in 7 studies, and are the most widely used measures in clinical practice.[283] These scales are objective; however, there is risk of inter-rater differences. If raters are not trained or trained differently, then reliability is decreased[298] which makes comparison of results from different studies challenging. Additionally, the Ashworth Scale may not be suitable for clinical trials of anti-spasticity agents because it is poorly related to simultaneous muscle reflex activity.[276,299] Three studies used the H/M ratio, the ratio between the maximum H reflex and maximum M response,[44] to assess spasticity. The H-reflex is a monosynaptic reflex and it activated by stimulating afferent nerve fibres.[44,300] It is similar to muscle stretch reflex, and is increased with spasticity.[44,300] A limitation of this measure is that it can be influenced by technical and patient factors. For example, the M response, the maximum response of a muscle when the motor nerve is directly stimulated, may be influenced by a number of factors (how relaxed the arm is, how warm the subject is, and the positioning of the probe).[44]

The Paced Auditory Serial Addition Test (PASAT) is a highly recommended measure for cognition, and it is included in the Multiple Sclerosis Functional Composite (MSFC).[40,59] Most cognitive function studies utilized the PASAT as their primary assessment measure. This test has good psychometric properties of internal consistency and test-re-test reliability and is highly sensitive.[301] However, interpretation of the PASAT must be done critically because this assessment is negatively affected by age, IQ, and math ability.[301] It is also susceptible to practice effects, therefore an improved or higher score may be due to either a practice effect or a treatment effect.[301]

Study quality was most often affected by lack of blinding, lack of a power calculation, non-randomized trial design, and industry sponsorship of studies. Blinding is a prominent challenge in cannabinoid trials, even with a matched placebo. Many subjects, especially prior *Cannabis* users,[288,302,303] notice the psychoactive adverse events (AEs) associated with CBM.[281,282] Twenty-seven studies made an attempt to blind their subjects, and clearly indicated

the blinding technique used. Of these twenty-seven, nineteen also indicated blinding of the assessor(s). However, despite blinding, recognizable adverse effects may have resulted in unblinding.[254] Four studies assessed the effectiveness of subject blinding, two assessed blinding of subjects as well as treating physicians (physicians responsible for monitoring dose, adverse effects and general medical care and safety) and three assessed blinding of those performing the assessment measures. In most cases, subjects and treating physicians were able to correctly identify if the subject was on active treatment or placebo.[62,67,250,251] However, assessors were not able to correctly identify the treatment group and there was no association between the assessor's opinion and the treatment used.[62,250,251] Therefore, it is less likely that objective measures would be impacted by unblinding or the placebo effect.[283]

Several studies (n=41) did not report a power calculation, and some of the trials that did were underpowered. The lack of a power calculation and inadequate sample size can lead to false negative results that are ultimately inconclusive.[304]

No included articles compared CBM to currently used treatments for MS symptoms or progression. Active comparators allow for a more realistic assessment of the potential for CMB in MS. As well, since many of the current medications used to treat MS symptoms often result in adverse effects similar to CBM (e.g. dizziness, drowsiness, and nausea),[100,305] there is less risk of bias from unblinding and/or the placebo effect.[281,282]

Both observational and RCTs were included in the review, although non-randomized studies were inherently of lower quality. However, observational studies, unlike RCTs, provide real-world results,[306] are often of longer duration than RCTs, and have increased generalizability. Because of this, observational studies are especially useful for assessing long-term effects of CBM.

While the sponsorship of studies does not affect the quality score or discount positive outcomes, it is important to note when interpreting results. In this review, industry sponsored studies often had higher quality scores, most likely due to adequate resources to ensure study quality, and increased experience in conducting interventional research. Twenty-three studies were sponsored by pharmaceutical companies, assessing spasticity (n=12), bladder dysfunction (n=1), cognition (n=1), pain (n=3), safety (n=4), and general symptoms (n=2); the majority were using nabiximols (Sativex).

Comparable to past systematic reviews,[98,99,296,307,308] CBM use resulted in frequent but mild adverse events (AEs) that were well-tolerated. Common AEs were fatigue, dizziness, nausea, and dry mouth. A concerning AE with CBM use is cognitive dysfunction. *Cannabis* use is associated with cognitive dysfunction, and interferes with brain development,[289–291] especially verbal memory.[309] Since cognition is negatively affected in MS,[310,311] there is increased risk of cognitive decline with cannabinoid use in the MS population.[312] However any observed cognitive dysfunction in those with MS using *Cannabis* cannot be solely attributed to *Cannabis,* as cognitive dysfunction is a symptom of the disease.[310,311] Additionally, delirium can occur in MS,[313] and this could also be potentiated or exacerbated with cannabinoids use.[314–316]

4.1 Limitations of the Current Study

Although the current systematic review presents a comprehensive overview of studies using a cannabinoid product for the treatment of any MS symptom, limitations exist. First, only English studies were included. Forty-four non-English articles were excluded and therefore their results were not considered in this review. Authors were not contacted for further information, and assessments and data extracted were based solely on information reported in the study.[245] Additionally, as with all systematic reviews, there is a risk of publication bias.[245] However, given that many of our studies reported null or negative findings, publication bias does not appear to be a concern in our case. Limitations also exist with the quality assessment tool. A modified Downs and Black checklist was used, with quality levels defined as good (≥20/28), fair (15-19/28) and poor (≤ 14/28).[247] However, lower quality scores have also been deemed acceptable in other reviews.[245,317] Related, the quality assessment itself is subjective, and challenging when studies have poor reporting.[245] The use of two independent reviewers, as well as a third reviewer to resolve any discrepancies helped to alleviate this issue.[245] Finally, the heterogeneity of studies precluded a meta-analysis of our data.

4.2 Future Directions

Future research on the role of CBM in MS should include high-quality, long-term studies evaluating adverse events, with a specific focus on cognitive dysfunction. Since individuals with MS are already at risk for cognitive decline, the use of CBM may worsen this,[312] and more research in this area is needed. More research is also needed on the potential for cannabinoids to treat MS disease progression, given the immunomodulatory and anti-inflammatory properties of cannabinoids, and in particular CBD.[154,157] Therefore, future research should also aim to increase clinical knowledge of other cannabinoid products/formulations, for example *Cannabis* oil and other CBD-prominent products.

While long-term side effects of cannabinoids in the MS population needs further research, current reported side effects of CBM (dizziness, nausea) are common to those seen with regularly used MS symptom medications.[98–100] Additionally, MS medications like baclofen must be taken for weeks before a full effect is seen,[100] while the effects of nabiximols are observed fifteen to forty-five minutes after administration.[155] Nabiximols can also be stopped suddenly without risk, unlike other MS medications,[99,100] as there are no direct withdrawal symptoms.[58] Finally, while cognitive dysfunction is a concern with cannabinoid use, common MS treatments (baclofen, tizanidine) may also affect cognition, although evidence is limited.[283,318] Therefore, when assessing the use of CBM in the MS population, it is important to assess both the positive and negative aspects of the treatment, and compare this to medications commonly used to treat MS and its associated symptoms. Finally, future work should evaluate the combination of cannabinoids with other MS medications, including the disease-modifying therapies to examine potential synergistic benefits or negative interactions.[308]

4.3 Conclusion

This systematic review concludes that cannabinoids may present a modest and variable reduction in subjective spasticity and pain in those living with MS. Future studies must be high-quality and long-term to provide robust evidence of the potential of CBM in MS, particularly for symptoms of bladder dysfunction, tremor, and balance/walking. Also, due to their immunomodulatory effects, future research should focus on the potential of cannabinoids for the

treatment of MS disease progression.[154,157] Cannabinoids appear to be safe in MS, as adverse events were generally mild and well-tolerated. However, more long-term studies are needed in order to assess the effect of cannabinoids on cognition in individuals with MS. Ultimately, more work needs to be done with respect to CBD products and MS, specifically its potential use in treating MS disease progression, and possible interactions between current MS medications and cannabinoids.

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Appendix A: Modified Downs and Black Quality Assessment Tool

Table A.1. Modified Downs and Black checklist [247]

Item	Criteria	Score
Reporting		
1	*Is the hypothesis/aim/objective of the study clearly described?*	Yes = 1 No = 0
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	*Are the characteristics of the patients included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0
5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.	Yes = 1 No = 0
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	*Have the characteristics of patients lost to follow-up been described?*	Yes = 1 No = 0

Table A.1. Modified Downs and Black checklist [247]

Item	Criteria	Score
	This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	Yes = 1 No = 0
External Validity		
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to Determine = 0
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to Determine = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to Determine = 0
Internal Validity - Bias		
14	*Was an attempt made to blind study subjects to the intervention they have received?*	Yes = 1 No = 0

Table A.1. Modified Downs and Black checklist [247]

Item	Criteria	Score
	For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Unable to Determine = 0
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Yes = 1 No = 0 Unable to Determine = 0
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to Determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients the answer should yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to Determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to Determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to Determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to Determine = 0

Table A.1. Modified Downs and Black checklist [247]

Item	Criteria	Score
Internal Validity – Confounding (Selection Bias)		
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.	Yes = 1 No = 0 Unable to Determine = 0
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?* For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to Determine = 0
23	*Were study subjects randomised to intervention groups?* Studies which state that subjects were randomised should be answered yes except where method of randomisation would not ensure random allocation. For example, alternate allocation would score no because it is predictable.	Yes = 1 No = 0 Unable to Determine = 0
24	*Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?* All non-randomised studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.	Yes = 1 No = 0 Unable to Determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?* This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.	Yes = 1 No = 0 Unable to Determine = 0
26	*Were losses of patients to follow-up taken into account?* If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the	Yes = 1 No = 0 Unable to Determine = 0

Table A.1. Modified Downs and Black checklist [247]

Item	Criteria	Score
	proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.	
Power		
27*	*Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?* Sample sizes have been calculated to detect a difference of x% and y%.	Yes = 1 No = 0 Unable to Determine = 0
*altered from Downs and Black checklist		